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Ambient Water Quality Criteria: Silver

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Silver

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
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CRITERIA DOCUMENT

SILVER

Criteria

Aquatic Life

For silver, the criterion to protect freshwater aquatic life derived using the Guidelines, is 0.0090 ug/l as a 24-hour average and the concentration should not exceed 1.9 ug/l at any time.

For silver, the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.26 ug/l as a 24-hour average and the concentration should not exceed 0.58 ug/l at any time.

Human Health

For silver, the criterion to protect human health from the toxic properties of silver ingested through water and through contaminated aquatic organisms is 10 ug/l.

BIBLIOGRAPHIC INFORMATION

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Criteria and Standards Div.

Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for silver. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no re , ...

KEYWORDS: *Water quality, *Toxicology, *Silver, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Water pollution effects(Plants).

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Introduction

Silver is a white ductile metal occurring naturally in the pure form and in ores. Principal uses of silver are in photographic materials, electroplating, as a conductor, in dental alloys, solder and braying alloys, paints, jewelry, silverware, coinage, and mirror production.

While metallic silver in the zero valence state is not considered to be toxic, most of its salts are toxic to a large number of organisms. Silver salts can combine with certain biological molecules and subsequently alter their properties. Silver is of some use as an antibacterial agent and has been shown to be bactericidal even in concentrations that are not great enough to precipitate proteins; the assumption is that silver is capable of interfering with essential metabolic processes in the bacterial cell (Goodman and Gilman, 1975). Concentrations from 0.001 to 500 µg/l of silver have been reported sufficient to sterilize water (McKee and Wolf, 1963). Upon ingestion, many silver salts are absorbed in the human circulatory system and deposited in various body tissues, resulting in generalized or sometimes localized gray pigmentation of the skin and mucous membranes known as argyria. There is no known method for removing silver from the tissues once deposited, and the effect is cumulative (Sax, 1975). This discoloration is due either to silver sulfide or metallic silver from the reduction of silver in tissue (Goodman and Gilman, 1975).

Toxic effects in aquatic organisms have been demonstrated for silver at very low concentrations. In freshwater fish, silver toxicity has been associated with changes in swimming behavior, decreased growth, and certain nervous system damage leading to mortality. Silver compounds have also been shown to cause ovarian cytopathic effects when administered orally to mice (Hadek, 1966). Overall effects of silver in non-human mammals include cytopathic, ventricular hypertrophy and pigmentation of body tissues (Olcott, 1948).

Silver (Ag) is a white metal that can exist in two valence states, Ag+ and Ag++. It has an atomic weight of 107.87. Solubilities of a few common silver salts in water are: AgCl, 1,930 ug/l; $AgNO_3$,2.5 x 10^9 ug/l; and AgI, 30 ug/l (Windoholz, 1976). Many silver salts are light-sensitive. Water or atmospheric oxygen have no effect on metallic silver; however, ozone, hydrogen sulfide, or sulfur will blacken it. Kopp (1969) reported that silver concentrations in samples of well and surface water in the U.S. ranged from 0.1 to 38 ug/l with a median of 2.6 ug/l. Silver can be easily removed from water supply sources by conventional coagulation and lime softening treatment methods (U.S. EPA, 1977).

REFERENCES

Goodman, L.S. and A. Gilman, eds. 1975. The pharmacological basis of therapeutics. 5th ed. Macmillan Publishing Co. Inc., New York.

Hadek, R. 1966. Preliminary report on the cellular effect of intravital silver in the mouse ovary. Jour. Ultrastruct. Res. 15: 66.

Kopp, J.F. 1969. The occurrence of trace elements in water. Page 59 _in_ D. Hemphill, ed. Proc. 3rd Annu. Conf. Trace Subst. Environ. Health. University of Missouri, Columbia, Mo.

McKee, J.E., and H.W. Wolf. 1963. Water quality. Publ. 3-A. Calif. State Water Resour. Control Board.

Olcott, C.T. 1948. Experimental argyrosis. _IV_. Morphologic changes in the experimental animal. Am. Jour. Pathol. 24: 813.

Sax, N.I. 1975. Dangerous properties of industrial materials. Van Nostrand and Reinhold Co., New York.

U.S. EPA. 1977. Manual of treatment techniques for meeting the interim primary drinking water regulations. EPA-600/8-77-005. U.S. Environ. Prot. Agency. Washington, D.C.

Windholz, M. ed. 1976. The Merck Index. 9th ed. Merck and Co., Inc. Rahway, N.J.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The chronic toxic effects of silver on the aquatic environment have not been given as much attention as many other heavy metals. However, data from existing literature support the fact that silver is very toxic to aquatic organisms. Despite the fact that silver is about the most toxic of the heavy metals, there are insufficient data to adequately evaluate even the effects of hardness on silver toxicity. Also, there are no data available on the toxicity of different forms of silver.

Acute Toxicity

Davies, et al. (1978) conducted 96-hour tests with rainbow trout in both hard (350 mg/l as $CaCO_3$) and soft water (26 mg/l as $CaCO_3$). The LC50 values were 6.5 and 13 ug/l for soft and hard water, respectively (Table 1). There are too few data to understand the relative importance of hardness and experimental variability on these nonreplicated results. The difference is quite small and at this time does not justify the derivation of hardness-related criteria for silver. Additionally, the datum by Hale (1977) for rainbow trout is not consistent (28.8 µg/l as the 96-hour LC50) with the relationship observed by Davies, et al. (1978). The geometric mean of adjusted LC50 values divided by the sensitivity factor (3.9) is the Final Acute Value for silver of 5.6 µg/l.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life 43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978) and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The adjusted 48-hour static EC50 for Daphnia magna is 1.3 µg/l (Table 2) and this result indicates that this species is more sensitive than the tested fish species and much more sensitive than the other invertebrate species tested. The adjusted 96-hour value for a rotifer is 1,186 µg/l. These data result in the Final Invertebrate Acute Value of 1.9 µg/l which also becomes the Final Acute Value.

Chronic Toxicity

Davies, et al. (1978) conducted the only chronic test with a freshwater species. The chronic value, obtained from an embryo-larval test with rainbow trout, is 0.06 µg/l (Table 3). This result was obtained in soft test water and is 0.009 of the comparable 96-hour value. These results indicate an appreciable difference between acute and chronic toxicity. Davies, et al. (1978) conducted an 18-month chronic test with rainbow trout (Table 6). This test began with embryos and there was no reproduction. There was 17.2 percent mortality at a concentration of 0.17 µg/l and no mortality at 0.09 µg/l. There was also premature hatching of eggs and reduced growth of fry at 0.17 µg/l.

The Final Fish Chronic Value is derived from the embryo-larval test result and is 0.0090 µg/l and, since there are no chronic data for invertebrate species, this concentration also is the Final Chronic Value.

Plant Effects

Hutchinson and Stokes (1975) observed growth retardation in the alga, *Chlorella vulgaris*, at silver concentrations between 10 and 60 µg/l (Table 4). A concentration of 2,000 µg/l was determined to be toxic to six additional algal species (Gratteau, 1970). The Final Plant Value is 10 µg/l.

Residues

Three insect species have been exposed to silver by Nehring (1973) and bioconcentration factors of 17 to 368 were determined (Table 5). Bluegill were also exposed during a 28-day test and there was no observed bioconcentration of silver at a water concentration of 0.03 µg/l (U.S. EPA, 1978).

Miscellaneous

The data by Davies, et al. (1978) have been discussed earlier. The 14-day LC50 values (Table 6) for two insect species ranged from less than 1 to 9 µg/l (Nehring, 1976) which indicates that these species are about as sensitive as the fish species (Table 1). No other data suggest adverse effects at concentrations lower than the Final Chronic Value.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of silver.

Final Fish Acute Value = 5.6 µg/l

Final Invertebrate Acute Value = 1.9 µg/l

Final Acute Value = 1.9 µg/l

Final Fish Chronic Value = 0.0090 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 10 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 0.0090 µg/l

0.44 x Final Acute Value = 0.84 µg/l

The maximum concentration of silver is the Final Acute Value of 1.9 µg/l and the 24-hour average concentration is the Final Chronic Value of 0.0090 µg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For silver the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.0090 µg/l as a 24-hour average and the concentration should not exceed 1.9 µg/l at any time.

Table 1. Freshwater fish acute values for silver

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Rainbow trout, Salmo gairdneri	FT	M	-	96	28.8	28.8	Hale, 1977
Rainbow trout, Salmo gairdneri	FT	M	26	96	6.5	6.5	Davies, et al. 1978
Rainbow trout, Salmo gairdneri	FT	M	350	96	13	13	Davies, et al. 1978
Bluegill, Lepomis macrochirus	S	U	-40	96	64	35	U.S. EPA, 1978

* FT = flow-through, S = static

** M = measured, U = unmeasured

Geometric mean of adjusted values = 21.70 µg/l $\frac{21.70}{3.9} = 5.6$ µg/l

Lowest value from a flow-through test with measured concentrations = 6.5 µg/l

Table 2. Freshwater invertebrate acute values for silver

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, *Daphnia magna*	S	U	-40	48	1.5	1.3	U.S. EPA, 1978
Rotifer, *Philodina acuticornis*	S	U	-	96	1,400	1,186	Buikema, et al. 1974

* S = static

** U = unmeasured

Geometric mean of adjusted values = 39 µg/l $\frac{39}{21}$ = 1.9 µg/l

Table 3. Freshwater fish chronic values for silver (Davies, et al. 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)	Hardness (mg/l as $CaCO_3$)
Rainbow trout, *Salmo gairdneri*.	E-L	0.09-0.17	0.06	28

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* E-L = embryo-larval

Geometric mean of chronic values = 0.06 µg/l $\frac{0.06}{6.7} = 0.0090$ µg/l

Lowest chronic value = 0.06 µg/l

Table 4. Freshwater plant effects for silver

Organism	Effect	Concentration (µg/l)	Reference
Alga, *Chlorella vulgaris*	Growth retardation	10-60	Hutchinson & Stokes, 1975
Alga, *Cylindrospermum licheniforme*	Toxic	2,000	Gratteau, 1970
Alga, *Microcystis aeruginosa*	Toxic	2,000	Gratteau, 1970
Alga, *Scenedesmus obliquus*	Toxic	2,000	Gratteau, 1970
Alga, *Chlorella variegata*	Toxic	2,000	Gratteau, 1970
Alga, *Gomphonema parvulum*	Toxic	2,000	Gratteau, 1970
Alga, *Nitzschia palea*	Toxic	2,000	Gratteau, 1970

Lowest plant value = 10 µg/l

Table 5. Freshwater residues for silver

Organism	Bioconcentration Factor*	Time (days)	Reference
Mayfly, *Ephemerella grandis*	42	5	Nehring, 1973
Mayfly, *Ephemerella grandis*	368	10	Nehring, 1973
Stonefly, *Claassenia sabulosa*	17	3	Nehring, 1973
Stonefly, *Pteronarcys californica*	23	6	Nehring, 1973
Stonefly, *Pteronarcys californica*	200	7	Nehring, 1973
Stonefly, *Pteronarcys californica*	112	15	Nehring, 1973
Bluegill, *Lepomis macrochirus*	0	28	U.S. EPA, 1978

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* Bioconcentration factors have been converted from dry weight to wet weight

Geometric mean of all non-zero concentration factors for all species = 55

Table 6. Other freshwater data for silver

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Cladoceran, *Daphnia magna*	24 hrs	LC50	274	1.5	Bringmann & Kühn, 1977
Mayfly, *Ephemerella grandis*	14 days	LC50	30-70	<1	Nehring, 1976
Stonefly, *Pteronarcys californica*	14 days	LC50	30-70	4-9	Nehring, 1976
Rainbow trout, *Salmo gairdneri*	18 mos	Mortality, premature hatching, reduced growth	28	0.17	Davies, et al. 1978
Fathead minnow, *Pimephales promelas*	96 hrs	100% mortality	49	75,260	Terhaar, et al. 1972
Fathead minnow, *Pimephales promelas*	96 hrs	100% mortality	49	782	Terhaar, et al. 1972
Fathead minnow, *Pimephales promelas*	96 hrs	80% mortality	49	635	Terhaar, et al. 1972
Fathead minnow, *Pimephales promelas*	96 hrs	60% mortality	49	64	Terhaar, et al. 1972
Fathead minnow, *Pimephales promelas*	96 hrs	75% mortality	49	250,000	Terhaar, et al. 1972
Largemouth bass, *Micropterus salmoides*	24 hrs	Lethal	-	70	Coleman & Cearley, 1974

SALTWATER ORGANISMS

Introduction

The silver data base for saltwater organisms is insufficient to determine the importance of salinity, temperature, and other water quality factors on the toxicity of this metal.

Acute Toxicity

Acute toxicity data are available only for four saltwater invertebrate species and range from 5.8 to 262 ug/l before and from 4.9 to 262 µg/l after adjustment for test conditions (Table 7). The American oyster was the most sensitive species tested and the mysid shrimp was the most resistant. The geometric mean of adjusted invertebrate acute values is 28.3 µg/l and when divided by the sensitivity factor (49) gives a Final Invertebrate Acute Value of 0.58 µg/l, a concentration one order of magnitude lower than the level of silver acutely toxic to larvae of the American oyster. Since there are no data for saltwater fish, the Final Invertebrate Acute Value (0.58 µg/l) becomes the Final Acute Value.

Chronic Toxicity

The chronic toxicity of silver has been determined (Table 8) based on a flow-through, life-cycle exposure of the mysid shrimp (Sosnowski and Gentile, Manuscript). In this experiment, groups of 20 juvenile shrimp were reared in each of five silver concentrations for 58 days at 20^{o} C and 30^{o}/oo salinity. Responses examined included time of appearance of first brood, times of first spawn, mean brood size (larvae/female), growth of larvae, and survival of first filial generation. No spawning occurred at 103 µg/l and time of spawning was delayed to 7 days at 33.3 µg/l. Brood size was statistically ($P<0.05$) smaller at 33.3 µg/l as compared to controls. Larval survival was unimpaired and was at least 95 percent in all cases and larval growth was not retarded at any test concentration.

The highest concentration of silver tested having no effect on growth, reproduction, and survival was 10.2 µg/l. This level is approximately 0.04 times the 96-hour LC50 (262 µg/l) determined for adults. The chronic value, when divided by the species sensitivity factor of 5.1 results in a Final Invertebrate Chronic Value of 3.6 µg/l. In the absence of data for fish species, this also becomes the Final Chronic Value.

Plant Effects

Information on the sensitivity of aquatic plants to silver is limited to the results of one test showing inhibition of growth after a 96-hour exposure to 130 µg/l (Table 9).

Residues

No information is available to provide a basis for determining a Residue Limited Toxicant Concentration for silver and saltwater organisms.

Miscellaneous

Most of the data included in Table 10 suggest no effects at concentrations lower than those at which acute toxicity occurs. However, egg development of the sea urchin (Soyer, 1963) was reduced at 0.5 µg/l, which is only slightly above the criterion for silver.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of silver.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 0.58 μg/l

Final Acute Value = 0.58 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 3.6 μg/l

Final Plant Value = 130 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 3.6 μg/l

0.44 x Final Acute Value = 0.26 μg/l

The maximum concentration of silver is the Final Acute Value of 0.58 μg/l and the 24-hour average concentration is 0.44 times the Final Acute Value or 0.26 μg/l. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For silver the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.26 μg/l as a 24-hour average and the concentration should not exceed 0.58 μg/l at any time.

Table 7. Marine invertebrate acute values for silver

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bay scallop (juvenile), *Argopecten irradians*	S	U	96	33	28	Nelson, et al. 1976
American oyster (larva), *Crassostrea virginica*	S	U	48	5.8	4.9	Calabrese, et al. 1973
Hard-shell clam (larva), *Mercenaria mercenaria*	S	U	48	21	17.8	Calabrese & Nelson, 1974
Mysid shrimp, *Mysidopsis bahia*	FT	M	96	262	262	Sosnowski & Gentile, Manuscript

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 28.3 μg/l $\frac{28.3}{49}$ = 0.58 μg/l

Lowest value from a flow-through test with measured concentration = 262 μg/l

Table 8. Marine invertebrate chronic values for silver (Sosnowski & Gentile, Manuscript)

Organism	Test	Limits (ug/l)	Chronic Value (ug/l)
Mysid shrimp, *Mysidopsis bahia*	LC*	10.2-33.3	18.4

* LC = life-cycle

Geometric mean of chronic value = 18.4 μg/l $\frac{18.4}{5.1}$ = 3.6 μg/l

Lowest chronic value = 18.4 μg/l

Table 9. Marine plant effects for silver (U.S. EPA, 1978)

Organism	Effect	Concentration (µg/l)
Alga, *Skeletonema costatum*	96-hr EC50 chlorophyll *a*	170
Alga, *Skeletonema costatum*	96-hr EC50 cell number	130

Lowest plant value = 130 µg/l

Table 10. Other marine data for silver

Organism	Test Duration	Effect	Result (ug/l)	Reference
Red alga (sporeling), *Plumaria elegans*	18 hrs	98% mortality	1,000	Boney, et al. 1959
Bay scallop (juvenile), *Argopecten irradians*	4 days	15% increased O_2 uptake	22	Nelson, et al. 1976
American oyster (larva), *Crassostrea virginica*	2 days	100% mortality	10	Calabrese, et al. 1973
American oyster (larva), *Crassostrea virginica*	12 days	50% mortality	25	Calabrese, et al. 1977
American oyster, *Crassostrea virginica*	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Hard-shell clam, *Mercenaria mercenaria*	2 days	100% mortality	45	Calabrese & Nelson, 1974
Hard-shell clam, *Mercenaria mercenaria*	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Hard-shell clam (larva), *Mercenaria mercenaria*	10 days	LC50	32	Calabrese, et al. 1977
Soft-shell clam, *Mya arenaria*	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Blue mussel, *Mytilus edulis*	4 days	Significant increase in oxygen consumption	100	Thurberg, et al. 1974
Mud snail, *Nassarius obsoletus*	3 days	Depression of oxygen consumption	500	MacInnes & Thurberg, 1974
Mud snail, *Nassarius obsoletus*	3 days	Distressed behavior, snail unable to move	250	MacInnes & Thurberg, 1974
Surf clam (larva), *Spisula solidissima*	15 days	Significant increase in oxygen consumption	50	Thurberg, et al. 1975
Surf clam (juvenile), *Spisula solidissima*	4 days	Significant increase in oxygen consumption	10	Thurberg, et al. 1975
Surf clam (adult), *Spisula solidissima*	4 days	Significant increase in oxygen consumption	50	Thurberg, et al. 1975

Table 10. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Common barnacle (adult), *Balanus balanoides*	2 days	90% mortality	400	Clarke, 1947
Common barnacle (adult), *Balanus balanoides*	5 days	90% mortality	200	Clarke, 1947
Sea urchin, *Arbacia lixula*	52 hrs	Reduced egg development significantly	0.5	Soyer, 1963
Mummichog (adult), *Fundulus heteroclitus*	4 days	*In vivo* inhibition of 3 liver enzymes	30	Jackim, et al. 1970
Mummichog (adult), *Fundulus heteroclitus*	2 days	Degeneration of lateral line and olfactory sensory structure	500	Gardner, 1975
Cunner, *Tautogolabrus adspersus*	4 days	Significant depression of oxygen consumption	120	Thurberg & Collier, 1977

Lowest value = 0.5 µg/l

REFERENCES

Boney, A.D., et al. 1959. The effects of various poisons on the growth and viability of sporelings of the red alga *Plumaria elegans* (Bonnem.) Schm. Biochem. Pharmacol. 2: 37.

Bringmann, V.G., and R. Kuhn. 1977. Report on the damaging action of water pollutants to *Daphnia magna*. Wasser- and Abwasser-Forschung 10. Jahrgang. Nr. 5/77: 161.

Buikema, A.L. Jr., et al. 1974. Evaluation of *Philodina acuticornis* (Rotifera) as a bioassay organism for heavy metals. Water Resources Bull. 10: 648.

Calabrese, A., and D.A. Nelson. 1974. Inhibition of embryonic development of the hard clam, *Mercenaria mercenaria* by heavy metals. Bull. Environ. Contam. Toxicol. 11: 92.

Calabrese, A., et al. 1973. The toxicity of heavy metals to the embryos of the American oyster (*Crassostrea virginica*). Mar. Biol. 18: 162.

Calabrese, A., et al. 1977. Effects of cadmium, mercury and silver on marine animals. Marine Fisheries Review. 39: 5.

Clarke, G.L. 1947. Poisoning and recovery in barnacles and mussels. Biol. Bull. 92: 73.

Coleman, R.L., and J. Cearley. 1974. Silver toxicity and accumulation in largemouth bass and bluegill. Bull. Environ. Contam. Toxicol. 12: 53.

Davies, P.H., et al. 1978. Toxicity of silver to rainbow trout (*Salmo gairdneri*). Water Res. 12: 113.

Fitzgerald, G.P. 1968. Compatibility of swimming pool algicides and bactericides. Water Sewage Works 115: 65.

Fitzgerald, G.P., and S.L. Faust. 1963. Factors affecting the algicidal and algistatic properties of copper. Appl. Microbiol. 11: 345.

Fitzgerald, G.P., and S.L. Faust. 1963. Bioassay for algicidal versus algistatic chemicals. Water Sewage Works 110: 296.

Gardner, G.R. 1975. Chemically induced lesions in estuarine or marine teleosts. Pages 657-693. *In*: W.E. Ribeline and G. Migaki (eds.). *The Pathology of Fishes* Madison. University of Wisconsin Press.

Gratteau, J.C. 1970. Potential algicides for the control of algae. Ref. No. 1970. Water Sewage Works p. R-24.

Hale, J.G. 1977. Toxic metal mining wastes. Bull. Environ. Contam. Toxicol. 17: 66.

Hutchinson, T.C., and P.M. Stokes. 1975. Heavy metal toxicity and algal bioassays. Water Quality Parameters. ASTM SPT 573: 320.

Jackim, E., et al. 1970. Effects of metal poisoning on five liver enzymes in the killifish (Fundulus heteroclitus). Jour. Fish. Res. Board Can. 27: 383.

MacInnes, J.R., and F.P. Thurberg. 1974. Effects of metals on the behavior and oxygen consumption of the mud snail. Mar. Poll. Bull. 4: 185.

Nehring, R.B. 1973. Heavy metal toxicity in two species of aquatic insects. Master's Thesis, Colorado State Univ., Fort Collins, Colorado. 82 p.

Nehring, R.B. 1976. Aquatic insects as biological monitors of heavy metal pollution. Bull. Environ. Contam. Toxicol. 15: 147.

Nelson, D.A., et al. 1976. Biological effects of heavy metals on juvenile bay scallops, Argopecten irradians, in short-term exposures. Bull. Environ. Contam. Toxicol. 16: 275.

Sosnowski, S.L., and J.H. Gentile. Chronic toxicity of copper and silver to the mysid shrimp Mysidopsis bahia. EPA-Environmental Research Lab, Narragansett, R.I. Manuscript.

Soyer, J. 1963. Contribution a l'etude des effects biologiques du mercure et de l'argent dans l'eau de mer. Vie et Milieu. 14: 1.

Stokes, P.M., et al. 1973. Heavy metal tolerance in algae isolated from polluted lakes near the Sudbury, Ontario smelters. Water Pollut. Res. in Can. 8: 178.

Terhaar, G.J., et al. 1972. Toxicity of photographic processing chemicals to fish. Photographic Sci. and Engr. 16: 370.

Thurberg, F.P., and R.S. Collier. 1977. Respiratory response of cunners to silver. Mar. Pollut. Bull. 8: 40.

Thurberg, F.P., et al. 1974. Effects of silver on oxygen consumption of bivalves at various salinities. Pages 67-78. In: F.J. Vernberg and W.B. Vernberg (eds.) Pollution and Physiology of Marine Organisms. N.Y., Academic Press.

Thurberg, F.P., et al. 1975. Respiratory response of larval, juvenile, and adult surf clams, Spisula solidissima, to silver. Pages 41-52. In: J.J. Cech, Jr., D.W. Bridges, and D.B. Horton (eds.). Respiration of Marine Organisms. South Portland, Me., TRIGOM Publ.

Tong, S.S.C., et al. 1974. Trace metals in Lake Cayuga lake trout (*Salvelinus namaycush*) in relation to age. Jour. Fish. Res. Board Can. 31: 238.

U.S. Environmental Protection Agency. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. EPA Contract No. 68-01-4646. U.S. Environ. Prot. Agency, Washington, D.C.

SILVER

Mammalian Toxicology and Human Health Effects

EXPOSURE

Silver is a frequent contaminant of normal human tissues, generally at $\leq$ 1 mg/kg in the ash (Tipton and Cook, 1963). For an extensive tabulation of silver concentrations in the tissues of normal individuals, disease victims, and people with argyria, see Smith and Carson (1977), pp. 54 to 60. Anspaegh, et al. (1971) of Lawrence Livermore Laboratory have also compiled data from the published literature on the silver content of human tissues. Most reported values have been based on ash weight or dry weight and are rather difficult to compare since analytical procedures at such low concentrations vary in their accuracies. Data in Table, adapted from Hamilton, et al. (1972/1973), however, seem to be in agreement with most reports.

Silver concentration in human tissues apparently increases with age. It has been detected, however, in human placentae (Mischel, 1956) and fetal livers (Robkin, et al. 1973). Absorption upon exposure or the extent of exposure itself may vary considerably among normals as reflected is tissue levels. For example, the silver content of the hair of school children from 21 school districts in Silesia, Poland, ranged from 0.23 to 1.96 mg/kg (average 0.69 mg/kg; analysis by neutron activation) (Dutkiewica, et al. 1978).

Ingestion from Water

Natural fresh waters contain an average 0.2 ug/liter silver, and seawater 0.24 µg/liter (Boyle, 1968). Water-analysis data from many literature sources have been adapted from Smith and Carson (1977) in Table 1.

Kopp and Kroner (1970) found silver in 6.6 percent of 1,577 surface water samples collected in the United States. Concentrations in samples containing silver varied from 0.1 to 38 µg/liter with a mean of 2.6 µg/liter. The highest silver concentration was in the Colorado River at Loma, Colorado. Upstream industries included an old gold-copper-silver mine; an oil shale extraction plant at Rigle; uranium plants at Rigle, Grand Junction, and Gunnison; and a gasoline and coke refinery 1 mile from Loma.

Another striking example of elevated silver concentrations was found in 280 miles of streams and lakes in the Lower North Canadian River (LNCR) Basin of Oklahoma. The range of silver concentrations varied from undetectable to 25 µg/liter in samples collected during all seasons. Water and sediment samples were collected at eight mainstream stations, eight tributary stream stations, and four Lake Eufaula stations. The LNCR also contained extraordinarily high concentrations of other trace elements and nutrients. The probable reason for the anomalously high silver concentrations was the low water volume in some of the sampling streams. For example, the maximum concentration of silver was detected on the Soldier Creek Tributary (pH 7), which drained wastes from the northeast corner of Tinker Air Force Base. Silver was never detected at the sampling station closest to the Henryeta zinc smelter, but even the zinc concentration was lowest there (Frank, 1969).

TABLE 1

Silver Content in Healthy Human Tissues in the United Kingdom
(Hamilton, et al. 1972/1973)

	No.	Ag, µg/g Wet Wt.
Blood (U.K. Master Mix)		0.01 ± 0.005
Blood (U.K.)	93	0.008 ± 0.0008
Whole brain	10	0.004 ± 0.002
Frontal lobe	2	0.003 ± 0.001
Basal ganglia	2	0.004 ± 0.002
Whole kidney	8	0.002 ± 0.0002
Cortex	8	0.001 ± 0.0002
Medulla	8	0.002 ± 0.0002
Liver	11	0.006 ± 0.002
Lung	11	0.002 ± 0.0001
Lymph nodes	6	0.001 ± 0.0002
Muscle	6	0.002 ± 0.0005
Testis	5	0.002 ± 0.0004
Ovary	6	0.002 ± 0.0005
Bone (rib) from patient who lived in:		
Hard water area	22	1.1 ± 0.2 (ash)
Soft water area	22	1.1 ± 0.2 (ash)

TABLE 2

Silver in Natural U.S. Waters

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Rainfall	-	-	0.002-0.216	St. Louis, Missouri		Rattonetti (1974)
Precipitation	0	0	0.02			
Precipitation (AgI seeded)	-	-	0.001-4.5	-	Typically 0.01-0.3 ppb Ag	Cooper & Jolly
Snowfall (AgI seeded)	-	-	0.11 (0.13 neutron activation anal.)	-		Warburton (1969)
Freshwater	-	-	0.01-0.7	-		Hawkes & Webb (1962)
			0.13	-		Bowen (1966)
Springs and surface freshwaters	-	-	0.2	all	Widely diffused, marked regional variations. Surface waters usually have less Ag than springs	Boyle (1968)
Hot springs: SO_2, NaCl, HCO_3^-, borate, sulfate carbonate	5.3-9.1	0	up to 43,000 in siliceous	Steamboat Springs, Nevada		Boyle (1968)
Steam well: NaCl, $CaCl_2$, KCl	-	-	100-300 in water up to 13,000,000 in residue	Niland, California		Boyle (1968)
Spring and well waters	-	36%	10	Near Salton Sea, California	Geothermal brines have higher concn. of Ag and other trace metals than municipal or industrial wastewaters. Two of these samples had Ag content in excess of drinking water standards.	Bradford (1971)
Desert well brines	-	50%	10			
Oil well brines	-	-	0.1	California		Boyle (1968)
Vadose mine waters: SiO_2, Mg, Fe, Al, Ca, Cu, Mn, SO_4	Acid	-	207	Comstock Lode, Nevada		Boyle (1968)
Deep mine waters: sulfate, carbonate	Alkaline to neutral	-	3.3	Comstock Lode, Nevada	Temperature 116-170°F	Boyle (1968)

Table 2 (Continued)

Silver in Natural U.S. Waters

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Seawater	-	-	0.15-2.9 (0.29) average	All	Run-off is of minor importance. Like Ba, Ag concentrates with increasing depth and in areas of high organic productivity. May be less concentrated near shores.	
Seawater	-	-	0.3	-		Lanford (1969)
Seawater	-	-	0.16	Gulf of Mexico		Bowen (1966)
Seawater	-	-	0.145	40 miles west of San Francisco		Boyle (1968)
Seawater	-	-	0.15-0.3	-		Boyle (1968)
Lakes	-	-	0.1-3.5	Maine		Boyle (1968)
Lakes	-	86%	0.1 (average) 6.0 (maximum)	California	Samples collected from 170 High Sierra Lakes.	Bradford, et al. (1968)
Lake, ground, and Ottawa River water	-	-	0.006-0.7	Near Chalk River Nuclear Laboratory		Merritt (1971)

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Agricultural drainage	-	100%	0.8 (1.0 maximum)	Coachella Valley, California		Bradford (1971)
Lakes	-	33%	10	Near Sudbury, Ontario	After 60 years of copper smelting	Stokes, et al. (1973)
Lakes, streams, and rivers	-		10-200 (in residues)	U.S.		Boyle (1968)
Surface waters	-	22.4%	0.10-3.0 (0.3 average)	California		Myers, et al. (1958)
Stream water	-	-	0.00006-0.0062	St. Louis, Missouri		Klein (1972)
Rivers	-	-	up to 1.0	North America and Norway		Boyle (1968)
Large rivers	-	-	0-0.94	North America		Boyle (1968)
U.S. river basins	-	6.6%	2.6 (38 maximum)	U.S.	Detection limits for Kopp & Kroner were ppb.	Kopp & Kroner Page (1974)
Northeast River Basin	-	14.3%	1.9 (6.0 maximum)	Northeastern U.S.	Includes New Jersey	Kopp & Kroner (1970)
St. Lawrence River	-	29.6%	2.6 (6.0 maximum)	Massena, New York		Kopp & Kroner (1970)
Hudson River	-	-	0.13-0.59	Green Island, New York		Durum & Hoffty (1971)
North Atlantic River Basin	-	5.3%	0.9 (2.5 maximum)	U.S.		Kopp & Kroner (1970)
Delaware River	-	11.1%	1.1 (8.2 maximum)	Trenton, New Jersey		Kopp & Kroner (1970)
Delaware River	-	7.03%	3	-		Kopp & Kroner (1967)
Susquehanna River	-	-	0-0.29	Conowingo, Maryland		D. & H. (1971)
Susquehanna River	-	-	0.39	-	Andelman (1973)	
Southeast River Basin	-	5.5%	0.4 (0.7 maximum)	U.S.		Kopp & Kroner (1970)
Apalachicola River	-	-	0.058-0.11	Near Bloustown, Florida		Durum & Haffty (1971)
Mobile River	-	-	0.085-0.28	Mt. Vernon Landing, Alabama		
Neuse River	-	-	0.52	North Carolina	Groundwater lithology: Slate	Andelman (1973)
Neuse River	-	-	0.56	North Carolina	Shale	Andelman (1973)

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Neuse River	-	-	0.25	North Carolina	Granite	Andelman (1973)
Neuse River	-	-	0.86	North Carolina	Shale and schist	Andelman (1973)
Neuse River	-	-	0.30	North Carolina	Cretaceous sand	Andelman (1973)
Neuse River	-	-	-	North Carolina	Tertiary lime	Andelman (1973)
Neuse River	-	-	0.37 (average)	North Carolina	Standard deviation = 49 based on samples taken at 25 locations.	Andelman (1973)
Tennessee River Basin	-	0%	-	Tennessee and adjacent areas		Kopp & Kroner (1970)
Ohio River Basin	-	5.4%	2.1 (8.2 maximum)	U.S.		Kopp & Kroner (1970)
Youghiogheny River	-	-	0.05-1.0	West Newton, Pennsylvania	These primary streams receive acid mine drainage, but Ag was not detected 50 miles downstream in Toronto, Ohio	Kopp & Kroner (1967)
Kiskimintas River	-	-	0.5-1.3	Apollo, Pennsylvania		
Allegheny River	-	5.0%	2.0	Pittsburgh, Pennsylvania		Kopp & Kroner (1970)
Monongahela River	-	8.3%	2.0 (4.7 maximum)	Pittsburgh, Pennsylvania		Kopp & Kroner (1970)
Monongahela River	-	5.0%	4.0	Pittsburgh, Pennsylvania		Kopp & Kroner (1967)
Kanawha River	-	12.9%	1.2 (3.0 maximum)	Winfield Dam, West Virginia		Kopp & Kroner (1970)
Ohio River		60%	0.6-1			Kopp & Kroner (1965)
Great Lakes		14	1			Kopp & Kroner (1965)
Lake Erie Basin	-	6.4%	5.3 (9.0 maximum)	U.S.		Kopp & Kroner (1970)
Cuyahoga River	-	0	ND	Cleveland, Ohio	Receives effluents from automotive, meat-packaging, and paper industries	Kopp & Kroner (1967)
Maumee River	-	12.5%	5.3 (9.0 maximum)	Toledo, Ohio	Travels from Ft. Wayne, Indiana through industrial complexes and receives agricultural, petrochemical and metal working wastes.	Kopp & Kroner (1970)
Maumee River	-	12.5%	3.6 (6.0 maximum)	Toledo, Ohio		
Upper Mississippi River Basin	-	5.4	3.4 (6.0 maximum)	U.S.		Kopp & Kroner (1970)

TABLE 2 (Continued)

Type of Water	pH	Detection Frequency	Ag Content (ppb)	Location	Remarks	Reference
Western Great Lakes Basin	-	9.1%	1.4	U.S.		Kopp & Kroner (1970)
Detroit River	-	-	1.0 (3.8 maximum)	Detroit, Michigan		Kopp & Kroner (1970)
Missouri River Basin	-	4.1%	1.2 (1.5 maximum)	U.S.		Kopp & Kroner (1970)
Southwest-Lower Mississippi Basin	-	4.5%	4.3 (9.0 maximum)	U.S.		Kopp & Kroner (1970)
Mississippi River	-	-	0. 0.22	Baton Rouge, Louisiana		Durum & Haffty (1961)
Mississippi River	-	-	0.26	-		Andelman (1975)
Mississippi River		12				Kopp & Kroner (1965)
Missouri River		57	0.2-20			Kopp & Kroner (1965)
Atchafalaya River	-	-	ND-0.33	Krotz Springs, Louisiana		Durum & Haffty (1961)
Colorado River Basin	-	18%	5.6 (38 maximum)	U.S.		Kopp & Kroner (1971)
Animas River	-	45%	2.9 (7.0 maximum)	Cedar Hill, New Mexico		Kopp & Kroner (1971)
Colorado River	-	13.6%	16 (38 maximum)	Loma, Colorado		Kopp & Kroner (1971)
Colorado River	-	0	ND			Kopp & Kroner (1965)
Colorado River	-	-	0-1.0	Yuma, Arizona		Durum & Haffty (1961)
Western Gulf Basin	-	4.3%	3.5 (6.6 maximum)	U.S.		Kopp & Kroner (1971)
Pacific Northwest Basin	-	8.6%	0.9 (3.7 maximum)	U.S.		Kopp & Kroner (1971)
Columbia River	-	-	0.09-0.15	Near The Dalles, Oregon		Durum & Haffty
Columbia River		0	0			Kopp & Kroner
Clearwater River	-	-	0.1	Lewiston, Idaho	1 occurrence	Kopp & Kroner
Pend Oreille River	-	-	0.2	Albeni Falls Dam, Idaho	1 occurrence	Kopp & Kroner
Snake River	-	-	0.5-1.3	Payette, Idaho	2 occurrences	Kopp & Kroner
Snake River	-	-	1.4	Wawawai, Washington	1 occurrence	Kopp & Kroner
California Basin	-	0	ND	California		Kopp & Kroner
Sacramento River	-	-	0-0.16	Sacramento, California		Durum & Haffty
San Fernando Valley	-	-	20	California	Estimated in wastewater	Bargman & Garber (1973)
Great Basin	-	5.3%	0.3	Nevada	1 occurrence	Kopp
Alaska	-	5.6%	1.1	Alaska		Kopp
Yukon River	-	-	0.20-0.31	Mountain Village, Alaska		Durum

Photoprocessing effluents usually contain $Ag(S_2O_3)_2^{3-}$, dissociation constant 3.5×10^{-14}, and sometimes insoluble AgBr (solubility product 4.8×10^{-13} at 25°C) or Ag_2S. Thus, under normal circumstances, there are no free silver ions. Municipal biological treatment plants receiving photoprocessing wastes have not suffered any loss in efficiency therefrom. Some photoprocessing plants have even installed biological treatment plants themselves with up to 5 mg Ag/liter in the water and 250 mg Ag/liter in the aeration tank sludge. Since silver was present predominantly as Ag_2S with small amounts of metallic silver, the biological system was not adversely affected. Eastman Kodak activated sludge plant effluent contained 1 mg Ag/liter; no soluble silver was detected (i.e., $<$ 20 µg/liter or $<$ 20 ppb). Of this soluble silver, only a very small fraction could be uncomplexed Ag^+.

The Genesee River in New York has received photoprocessing effluents for approximately 70 years. In 1973, on most sampling dates from May 31 to October 17, it contained 20 µg/liter silver. However, levels of 90 to 260 µg/liter were detected in June. Sediments contained up to 150 mg/kg silver dry weight. Raw Lake Ontario water at the Eastman Kodak intake pipe contained 1 µg/liter silver (Bard, et al. 1976).

At 0.04 g Ag/liter and 0.01 g H_2S+HS^- per liter, AgSH is the major silver species normally present in freshwater, being present in concentrations up to 10-fold greater than the concentration of Ag^+ and AgCl. In seawater, there is more $AgCl_2^-$ than AgSH and Ag^+ concentrations are trivial.

Other species of minor or negligible importance in seawater are AgBr, $Ag(SH)_2^-$, AgF, AgOH, AgI, $AgNO_3$, $Ag(NO_2)_2^-$, and $AgSO_4$. The waters are oversaturated with silver by 7 to 12 times what is expected from available thermodynamic data (Jenne, et al. 1977).

The silver content of natural precipitates (i.e., stream sediments, etc.) has been discussed by Boyle (1968). The silver content of U.S. natural precipitates ranges from nil to 1,160 mg/kg. Turekian found 0.4 to 15.0 mg/kg silver in the suspended matter of 18 U.S. rivers. The Susquehanna River in Pennsylvania, which contained the highest concentration of silver, was estimated to be transporting 4.5 tons* of silver per year to the ocean (Turekian and Scott, 1967).

In the Lower North Canadian River (LNCR), the range of silver content in the ash of total suspended solids (silt plus microorganisms) was from undetected to 0.008 mg/kg, except at the station where the highest silver concentration was found in the water. Here, the silver content ranged from 15 to 50 mg/kg in the ash (Frank, 1974).

Silver concentrations of 0.05 to 45 µg/liter have been found in effluents from municipal waste treatment plants. Silver concentrations as high as 900 mg/kg in sewage sludge have been reported (Smith and Carson, 1977).

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* A mathematical error in the calculations lead to the report itself stating 45 tons.

Bruland, et al. (1974) studied the extent of metal pollution in the Southern California Coastal Zone, which receives Los Angeles area sewage. The average flux of anthropogenic silver into the sediments of the California Coastal Basin was estimated to be 50 percent greater than the average flux of natural silver (0.09 versus 0.06 $\mu g/cm^2$/year). The flux of anthropogenic silver to the sediments was calculated to be 11 MT/year/12,000 km^2, with the chief source being the municipal wastewaters (15 MT/year/12,000 km^2), rather than the storm water plus dry weather flow or the washout fluxes (1 and 5 MT/year/12,000 $km/^2$, respectively). Extraction studies indicated that the silver in these sediments occurred predominately as sulfides or bound to the organic phase.

The concentrations of silver in the wastewater particulates were 32 to 130 (average 70) mg/kg compared with about 6 mg/kg for the sediments in the basins receiving them. (The sediments were collected at 75 to 890 m from the sewage outfalls.)

High concentrations of mercury, silver, chromium, and zinc were recently found in the sediments downstream from the Vint Hill Farms Station military reservation. Although the sediment contamination extends for 2 miles in South Run in eastern Fauquier County, Virginia, which runs into Lake Manassas, the Manassas water treatment plant is able to remove the metals because of the water insolubility of the chemical forms present. There is concern, however, about heavy metal bioaccumulation in fish (Toxic Materials News, 1978).

TABLE 3

Silver in City Water Supplies

Ag Content (ppb)	Location	Remarks	Reference
0.23 (7.0 maximum)			Cannon & Hopps (1971)
50 (maximum)	U.S.	Maximum allowable Ag content of drinking water according to Federal Water Pollution Control Administration.	Kopp & Kroner (1970)
8 (average) 30 (maximum observed)	U.S.	2,595 samples of 956 municipal water supplies.	Taylor (1971)
ND - 0.35	Birmingham, Alabama		Durfor & Becker (1962)
0.09	Mobile, Alabama		Durfor & Becker (1962)
ND - 0.31	Montgomery, Alabama		Durfor & Becker (1962)
0.53 - 0.92	Phoenix, Arizona		Durfor & Becker (1962)
ND - 0.54	Tucson, Arizona		Durfor & Becker (1962)
ND - 0.40	Long Beach, California		Durfor & Becker (1962)
0.3	Los Angeles, California		Durfor & Becker (1962)
0.4 - 0.7	Los Angeles, California		Bargmon & Gorber (1973)
0.06	Oakland, California		Durfor & Becker (1962)
0.1 - 0.2	Sacramento, California		Durfor & Becker (1962)
0.78	San Diego, California		Durfor & Becker (1962)
0.06 - 0.08	San Francisco, California		Durfor & Becker (1962)
0.32	San Jose, California		Durfor & Becker (1962)
ND - 0.26	Denver, Colorado		Durfor & Becker (1962)
0.29	Hartford, Connecticut		Durfor & Becker (1962)
0.14 - 0.30	New Haven, Connecticut		Durfor & Becker (1962)
0.25 - 0.28	Washington, D.C.		Durfor & Becker (1962)
ND - 0.49	Jacksonville, Florida		Durfor & Becker (1962)
ND - 0.50	Miami, Florida		Durfor & Becker (1962)
ND - 0.21	St. Petersburg, Florida		Durfor & Becker (1962)
0.55	Tampa, Florida		Durfor & Becker (1962)
0.03 - 0.07	Atlanta, Georgia		Durfor & Becker (1962)
0.05 - 0.26	Savannah, Georgia		Durfor & Becker (1962)
0.26 - 0.34	Honolulu, Hawaii		Durfor & Becker (1962)
0 - 9 (100%) 0 - 1 (74%) 2 - 5 (22%)	Chicago, Illinois distribution points (maximum 2 ppb at the treatment plants)		McCabe (1969)
0.2 - 0.27	Chicago, Illinois		Durfor & Becker (1962)
0.5 - 0.59	Rockford, Illinois		Durfor & Becker (1962)
0.29	Evansville, Indiana		Durfor & Becker (1962)

TABLE 3 (Continued)

Ag Content (ppb)	Location	Remarks	Reference
0.2 - 0.54	Fort Wayne, Indiana		Durfor & Becker (1962)
0.24	Gary-Hobart, Indiana		Durfor & Becker (1962)
ND - 0.39	Indianapolis, Indiana		Durfor & Becker (1962)
0.24 - 0.48	South Bend, Indiana		Durfor & Becker (1962)
0.30	Des Moines, Iowa		Durfor & Becker (1962)
0.2 - 0.3	Louisville, Kentucky		Durfor & Becker (1962)
0.30 - 0.80	Baton Rouge, Louisiana		Durfor & Becker (1962)
0.25 - 7.0	New Orleans, Louisia		Durfor & Becker (1962)
0.18 - 0.24	shreveport, Louisiana		Durfor & Becker (1962)
0.13 - 0.74	Baltimore, Maryland		Durfor & Becker (1962)
0.18	Boston, Massachusetts		Durfor & Becker (1962)
0.14 - 0.49	Springfield, Massachusetts		Durfor & Becker (1962)
0.06	Worcester, Massachusetts		Durfor & Becker (1962)
0.21 - 0.22	Detroit, Michigan		Durfor & Becker (1962)
0.25 - 0.53	Flint, Michigan		Durfor & Becker (1962)
0.23 - 0.25	Grand Rapids, Michigan		Durfor & Becker (1962)
0.15 - 0.48	Minneapolis, Minnesota		Durfor & Becker (1962)
0.17 - 0.34	St. Paul, Minnesota		Durfor & Becker (1962)
0.68	Jackson, Mississippi		Durfor & Becker (1962)
0.28 - 0.56	Kansas City, Missouri		Durfor & Becker (1962)
0.22 - 0.23	St. Louis, Missouri		Durfor & Becker (1962)
0.3	St. Louis, Missouri	Finished Water	
0.41	Lincoln, Nebraska		Durfor & Becker (1962)
0.46	Omaha, Nebraska		Durfor & Becker (1962)
0.09	Jersey City (contiguous with Paterson and Newark)		Durfor & Becker (1962)
0.09 - 0.38	Newark, New Jersey		Durfor & Becker (1962)
0.09 - 0.09	Paterson, New Jersey		Durfor & Becker (1962)
ND - 0.5	Albuquerque, New Mexico		Durfor & Becker (1962)
0.07 - 0.12	Albany, New York		Durfor & Becker (1962)
0.26	Buffalo, New York		Durfor & Becker (1962)
0.23 - 0.39	New York City, New York		Durfor & Becker (1962)
0.14 - 0.30	Rochester, New York		Durfor & Becker (1962)
0.19	Syracuse, New York		Durfor & Becker (1962)
0.32 - 0.41	Yonkers, New York		Durfor & Becker (1962)
0.04 - 0.17	Charlotte, North Carolina		Durfor & Becker (1962)
0.17	Akron, Ohio		Durfor & Becker (1962)
0.29	Cincinnati, Ohio		Durfor & Becker (1962)
0.23	Cleveland, Ohio		Durfor & Becker (1962)
ND - 0.26	Columbus, Ohio		Durfor & Becker (1962)
1.1	Dayton, Ohio		Durfor & Becker (1962)

TABLE 3 (Concluded)

Ag Content (ppb)	Location	Remarks	Reference
0.16	Toledo, Ohio		Durfor & Becker (1962)
0.23	Youngstown, ohio		Durfor & Becker (1962)
0.54 - 0.76	Oklahoma City, Oklahoma		Durfor & Becker (1962)
0.19 - 0.20	Tulsa, Oklahoma		Durfor & Becker (1962)
0.02	Portland, Oregon		Durfor & Becker (1962)
0.26	Erie, Pennsylvania		Durfor & Becker (1962)
0.15 - 0.17	Philadelphia, Pennsylvania		Durfor & Becker (1962)
0.12 - 0.19	Pittsburgh, Pennsylvania		Durfor & Becker (1962)
0.07	Providence, Rhode Island		Durfor & Becker (1962)
ND - 0.24	Chattanooga, Tennessee		Durfor & Becker (1962)
ND - 0.19	Memphis, Tennessee		Durfor & Becker (1962)
0.16	Nashville, Tennessee		Durfor & Becker (1962)
ND - 0.29	Austin, Texas		Durfor & Becker (1962)
0.15 - 0.29	Dallas, Texas		Durfor & Becker (1962)
ND - 0.86	El Paso, Texas		Durfor & Becker (1962)
ND - 0.15	Houston, Texas		Durfor & Becker (1962)
ND - 1.5	Lubbock, Texas	A well	Durfor & Becker (1962)
0.27 - 0.54	Salt Lake City, Utah		Durfor & Becker (1962)
0.10 - 0.15	Norfolk, Virginia		Durfor & Becker (1962)
0.10	Richmond, Virginia		Durfor & Becker (1962)
0.05 - 0.06	Seattle, Washington		Durfor & Becker (1962)
0.26 - 0.53	Spokane, Washington		Durfor & Becker (1962)
0.05	Tacoma, Washington		Durfor & Becker (1962)
0.5	Madison, Wisconsin		Durfor & Becker (1962)
0.24 - 0.25	Milwaukee, Wisconsin		Durfor & Becker (1962)

The silver concentration in sediments is important because bottom-feeding mollusks, etc., tend to concentrate silver. Luoma and Jenne (1977) in laboratory studies determined that the uptake of silver bound to various typical sediment species--by the clam Macoma balthica depended on the particular sediment species to which it was bound. The concentration factor for sediment-bound $^{110\underline{m}}Ag$ (dry clam tissue/dry sediment) was 3.667 to 6.140 from calcite; 0.395 to 0.850 from $MnO_{\underline{x}}$; 0.043 to 0.146 from $Fe_{\underline{x}}O_{\underline{y}}$; 0.034 to 0.076 from biogenic $CaCO_3$; and 0.028 to 0.030 from organics. The percent of $^{110\underline{m}}Ag$ in the soft tissues of the clam was 42.6 to 57.0 (average 54.4 percent). In these experiments, the sediment-bound silver contributed somewhat more silver to the clam tissue than did solute silver (0.034 to 0.552 mg/kg versus 0.004 to 0.135 mg/kg in soft tissues).

Of 380 finished waters, 6.1 percent were found to contain silver at concentrations varying from 0.3 to 5 µg/liter (mean 2.2 µg/liter). Table 3 shows the silver content of water supplies for several U.S. cities. The silver content of these water supplies did not exceed the U.S. drinking water limits for maximum allowable concentration of silver, 0.05 mg/liter (Kopp, 1969). In another study, the maximum concentration of silver found in 2,595 distribution samples from 959 public water supply systems was 26 µg/liter. No silver was found in waters having pH $\leq$ 8, while for those at pH $\leq$ 8.0, the average silver content was 1 µg/liter.

Of Chicago water samples, 15 percent showed increased concentrations of silver after leaving the water treatment plant (McCabe, 1970).*

In 1935, Braidech and Emery reported 0.010 to 0.200 mg/kg silver (average 0.080 mg/kg) in the solid residues of all 24 city water supplies they studied. The highest value was from Denver, Colorado.

In a survey of metal concentrations in the drinking (tap) waters of Canadian communities, silver was found in 0.1 percent of the 239 sampled waters (detection limit of neutron activation analysis was 0.001 to 0.005 µg liter) (Neri, et al. 1975).

Tapwater in the Boston metropolitan area contained 0.010 mg/l silver in 896 samples; i.e., silver was not detected although Cu, Zn, Pb, and Fe were often present in the soft water of the area due to corrosion of pipe materials (Karalekas, et al. 1976).

Silver is used to purify potable water for Swiss ski resorts, German breweries, soft drink bottlers, British ships, Shell Oil Company tankers, drilling rigs, and over half the world's airlines including Pan Am and American. In the United States, the number of companies registered by the U.S. Environmental Protection Agency (EPA) to produce silver-containing water filters grew to 19 by February, 1978, from 10 only 2 years before. At least one water filter has been widely promoted by television advertising in the United States for home use. The units of Katadyn Products, Ltd., in Switzerland either produce silver ions anodically or by the slight dissolution of metallic silver impregnated on fine-porosity ceramic filters. They have been approved by the Swiss government for 38 years, requiring less than 200 µg/liter for their antimicrobial action (Silver Institute, 1976a, 1977b, 1978).

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* Silver contents in distribution samples (i.e., tapwater) may be higher than the finished waters from the treatment plant because of the preferred use of tin-silver solders for joining copper pipes in the home, office, or factory. In addition, American Standard, Inc. connects copper pipes for hot and cold water with tin-silver solder during the assembly of kitchen and bathroom appliances (Silver Institute, 1976b).

The Soviets have found silver ions at concentrations of 100 to 200 µg/liter to be safe, stable, and long-lasting for purification of polluted water for drinking in the Soviet space ship and orbiting station program. After animal tests showed these concentrations to be nondetrimental, year-long human volunteer studies confirmed the results (Silver Institute, 1973b). Silver sterilizers producing 100 to 200 µg/liter silver ions were also used on the Apollo Spacecraft waste and potable water systems (Albright, et al. 1967).

Ingestion from Food

Silver is a normal trace constituent of many organisms (Boyle, 1968). The ash of higher plants usually is found to contain $<$ 1 ppm silver, while the ash of terrestrial plants in general usually contains about 0.2 ppm silver. Higher values occur in trees, shrubs, and other terrestrial plants near regions of silver mineralization. Seeds, nuts, and fruits generally have higher silver contents than other plant parts (Smith and Carson, 1977).

Snyder, et al. (1975) estimated that the average intake of silver by Reference Man is 70 µg/day, based on a review of the literature. Kehoe, et al. (1940) had determined that daily dietary intake of humans in the U.S. was 88 µg/day. Tipton, et al. (1966) found the average daily intake of silver in the diets of a man and a woman in the U.S. were 35 μg and 40 μg silver, respectively. Hamilton and Minski (1972/1973) determined that the average daily human dietary intake of silver in the United Kingdom was 27 ± 17 μg. No consideration was given to intake from water used for cooking foods, making beverages, or drinking. Clemente, et al. (1977) reported that the average silver intake in the diets of three Italian populations was 0.4 μg/day as determined by neutron activation analysis. Five-day fecal samples of the population which had a silver intake of up to 7 μg/day showed a range of 1.1 to 202 μg/day (average 30 μg/day). Some source of pollution was felt to be the cause of greater metal intake. The latter population came from a large town in central Italy, whose major source of pollution was automotive engine exhaust.

Murthy and Rhea (1968) of the U.S. Public Health Service in Cincinnati determined by atomic absorption analysis 0.027 to 0.054 mg/kg (average) silver in cows' milk as market samples collected from various U.S. cities. The silver content did not vary significantly between cities, but there was a significant difference between quarterly sampling periods in the Southeastern states. The national weighted average was 0.047 ± 0.007 mg/kg. Milk from 32 cows on farms serving Cincinnati contained 0.037 to 0.059 mg/kg silver (average 0.047 ± 0.006 mg/kg).

Table 4 lists the silver concentration in several food items.

^{110m}Ag is an activation product produced during nuclear fission. The concentration factors* from lichen to caribou

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* Ratio of ^{110m}Ag activity per unit wet weight of tissue activity per unit wet weight of lichen.

TABLE 4

Silver in Some Foods

Type of Food	Range of Average Silver Concentrations, mg/kg	Reference
Beef	0.004-0.024	Armour Research Foundation (1952); Mitteldorf and Landon (1952)
Beef liver (SRM 1577)	0.005-0.194 (same sample by three laboratories)	Masironi (1974)
Pork	0.007-0.012	Armour Research Foundation (1952)
Mutton and lamb	0.006-0.011	Armour Research Foundation (1952)
Milk powder	0.010 ± 0.04	Schelenz (1977)
Potato powder	0.015 ± 0.005	Schelenz (1977)
Sugars		Hamilton and Minski (1972; 1973)
Brown (Barbados)	0.03	
Demerara	0.004	
Refined	<0.001	
Granulated	0.002	
Mollusks	0.1-10.0 (dry weight)	Boyle (1968); Cooper and Jolly (1970)
Crustaceans	≤ 2.0 (dry weight)	Boyle (1968)
Trout (Lake Cayuga, New York)	0.48-0.68 (dry weight)	Tong, et al. (1974)
Mushrooms	"Up to several hundred" (dry weight)	Cooper and Jolly (1970)
Wheat (*Triticum* spp.)	0.5 (dry weight)	Kent-Jones and Amos (1957)
Bran	1.0 (dry weight)	
Flour	0.4 (dry weight)	
Coffee beans	0.02 (dry weight)	Vanselow (1966)
Tea (*Camellia sinensis*)	< 0.20-2.00 (dry weight)	Vanselow (1966)

or reindeer estimated by Hanson, et al. (1966, cited by Garner) for ^{110m}Ag in muscle were 0.3; for liver, 80; for kidney, 1.3; and for bone, 3. Beattie and Bryant (1970) had estimated that 15 percent of the total ^{111}Ag dose from activation products would be received in a 30-year period starting in infancy by the forage-cow-milk pathway.

Sewage-sludge amended soils may have 10 times or more silver than normal and may increase human intake of silver by its incorporation into food crops in greater than normal amounts ince silver uptake by plants appears to be directly related to its soil concentration (Cooper and Jolly, 1969). Addition of phosphate to soil contaminated with silver, however, reduces its plant availability (Dawson, 1974).

It is likely that the silver content would be increased in the meat of animals pastured or fed grains raised on contaminated soils.* At least one study, however, has indicated that the transfer of iron, copper, nickel, chromium, zinc, cadmium, and lead from sewage-sludge amended soils to dairy or beef cattle milk or tissues is minimal (Nelmes, et al. 1974).

Among aquatic species harvested for food, the hepatopancreas and nephridial organs of brachiopods, mollusks, and arthropods, particularly crustaceans, accumulate heavy metals. The glandular tissue of the liver of fishes and all other vertebrates concentrates metals (Vinogradov, 1953). Marine animals accumulate silver in concentrations which are higher than their environment. Clams and scallops growing near municipal sewage-sludge dumping sites accumulate higher concentrations of silver than do those growing where the concentrations of silver are lower (Toxic Materials News, 1975). The enrichment factor calculated by Noddack and Noddack (1939) for silver in marine animals over seawater is 22,000. The dead bodies of animals in reducing environments will contribute their silver to sediments, a major factor in the geochemical cycle of silver (Boyle, 1968).

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* If a 0.25-lb portion of meat contains 0.007 mg/kg, the 0.0065 mg silver consumed would represent only about 1 to 2 percent of the low silver dietary intake reported by Tipton, et al. (1966).

Besides food and drinking water, silver is possibly ingested from dissolution of silver dental amalgams in the mouth by saliva. Wyckoff and Hunter (1956) qualitatively detected silver spectrographically in the erythrocyte contents and possibly in the plasma and erythrocyte membrane (ghosts) of two people who had dental fillings. No silver was detected in a preliminary examination of another person who did not have any dental fillings. Reynolds and Warner (1977) concluded that the corrosion product of Ag_3Sn amalgams after only 30-min exposure to human saliva *in vitro* was $SnCl_4$.

Some silver may be released to soft tissues from silver amalgam dental fillings when placed in unlined cavities according to Leirskar (1974), who found by atomic absorption analysis that there was definite release *in vitro* of zinc and mercury into a human monolayer epithelial cell culture (22 ug Zn/m and 0.0177 to 0.0196 ug Hg/ml); some silver also appeared to have been released. Silver amalgam cultures contained 0.02 ug Ag/ml after 3 days (the detection limit for silver, however, was 0.01 ug/ml--much higher than that for mercury). Leirskar cited three other studies that reported diffusion of amalgam constituent metals, including silver, into adjacent dentin.

TABLE 5

Silver in Ground-Level Atmospheric Aerosols 6,7

City	Date	Aerosol Silver Concentration		
		ng/m^3	ppb	
Heidelberg, Germany	April - June, 1971	4.2	0.0032	Bogen (1974)
Niles, Michigan	June, 1969	1	0.00077	Bogen (1974)
Northwest Indiana	1969	1.5		Dams, et al. (1971)
East Chicago, Illinois	June, 1969	2.4	0.0019	Bogen (1974)
Chicago, Illinois	1968	4.3		Brar, et al. (1970)
Oak Ridge, Tennessee Vicinity: Walker Branch Watershed	July, 1974	0.17	0.00013	Andren, et al. (1974)
Chadron, Nebraska	1973	average 0.15 (range 0.02 to 1.8)		Struempler (1975)
	June - Sept., 1973	0.14		
	June - Sept., 1974	0.04		
Washington, D.C.	1974	1.1		Trout (1975) cited by Greenberg, et al. (1978)
San Francisco	1970	0.15		John, et al. (1973) cited by Greenberg, et al. (1978)
Kellogg, Idaho (city hall)		10.5[a/] (range 0.936 to 36.5)		Ragaini, et al. (1977)

[a/] Average Concentrations of mercury, antimony, cadmium, zinc, and lead ranged from 113 to 10,800 ng/m^3. The nearby Bunker Hill smelter smelts silver-rich lead concentrates and roasts zinc concentrates.

Inhalation

Silver is generally a very minor constituent of ambient aerosols. Table 5, gives a reasonably representative sample of silver determinations in air, although it is by no means exhaustive, since reports of nuclear activation analyses of atmospheric particulates are proliferating rapidly. Interestingly enough, Chadron, Nebraska, which has a population of 6,000 in a sparsely inhabited region, had the same average ambient air concentration of silver in 1973--0.15 ng/m^3--as San Francisco had in 1970. A non-industrial city, Washington, D.C., had a concentration of 1.1 ng/m^3 in 1974. The very industrialized urban environment of Chicago, Illinois, had an ambient atmospheric silver concentration only four times higher (4.3 ng/m^3). Even one of the sites having an expectedly high silver concentration in the silver-rich Coeur d'Alene region of northern Idaho had only an order of magnitude greater silver concentration (average 10.5 ng/m^3) than a nonindustrialized large population center.

Smith and Carson (1977) estimated that total annual atmospheric silver emissions in the United States in the early 1970's were about 340 short tons or about 310,000 kg. About 60 percent of this total was distributed equally between iron and steel production and cement manufacture, about 12 percent each was due to fossil fuel burning and nonferrous metal smelting and refining, and about 7 percent was due to urban refuse incineration. Another published estimate for total annual silver emissions was 417 short tons (Dulka and Risby, 1976, citing a personal communication from V. Duffield, 1975).

Greenberg, et al. (1978) attributed to urban refuse incineration a much higher share of the total silver content in the urban particulate load. They estimated that the contribution of silver from refuse incineration to ambient urban air is 1.7 ng/m^3.

Steel mills have been implicated as the major source of aerosol silver, yet the following data (Harrison, et al. 1971) do not seem to support this contention. Air particulate samples were collected June 11 and 12, 1969, at 25 stations in the northwest Indiana area, including the Hammond-East Chicago-Gary-Whiting metropolitan complex. At that time, the entire sampling area contained three large steel mills as well as four large petroleum refineries, foundries, steel fabricators, chemical plants, a large cement-manufacturing plant, and two large power utilities. The silver concentrations in the area ranged from <0.5 to 5 ng/m^3. The maximum silver concentration was found at a station downwind from the steel mills. High silver concentrations did not occur at the same stations where maximum iron levels occurred. Therefore, steel manufacturing was not believed to be the major source of silver found in these samples (Dams, et al. 1971).

At another station, in Gary, near the third steel mill, secondary maxima for iron and eight other metals were associated with a silver concentration 4 ng/m^3. The direction of the unusually strong, steady wind prevailing during the sampling was such that most of the shoreline steel and cement plant emissions (85 percent and 12.5 percent, respectively, of the area's industrial particulate emissions) may have been swept directly over the lake so that the observed air concentrations at stations nearest them were much lower than normal (Dams, et al. 1971). On April 4, 1968, 1 day after general rainfall, with wind blowing at 34 km/hr, the silver concentrations in surface air samples from 22 aerosol-collecting stations in Chicago, Illinois, ranged from 0.18 to 7.0 ng/m^3 (average 4.3 ng/m^3). Correlation coefficients for silver with other elements or dust were not determined (Brar, et al 1970).

Another source of silver to ambient air is from volatile emission from certain trees. Curtin, et al. (1974/75) traced the path of elements from the soil and mull (the humus-rich layer of mixed organic and mineral matter 3-to 8-cm thick beneath individual trees) into the needles, twigs, and volatile exudates of lodgepole pine, Engelmann spruce, and Douglas fir in Idaho Springs, Colorado and Stibnite, Idaho. Silver was not detected in the soil; but in Colorado, its highest concentrations were in the mull ash under all species. In Idaho, the silver concentration was highest in the twigs of the pine and spruce and in the exudate residue of the Douglas fir. Presumably, the metals in the exudate are complexed by terpenes and appear in the blue haze of forested areas.

Nadkarni and Ehmann (1969) determined 2.61 mg/kg silver in a reference cigarette tobacco* by neutron activation analysis and 2.87 mg/kg silver in the paper. Nadkarni, et al. (1970) found 0.27 ± 0.18 mg/kg silver in a filter cigarette of a popular brand and 0.18± 0.03 mg/kg in a non-filter cigarette of the same brand; there was 0.48 mg/kg silver in 1.65 g of smoke condensate from 500 filter cigarettes and 0.30 mg/kg silver in 14.5 g condensate from 500 nonfilter cigarettes. Only 0.60 percent of the silver transferred into the mainstream smoke condensate of the filter cigarette; 4.4 percent transferred from the nonfilter cigarette. The amount of silver inhaled into the lungs in the mainstream smoke per cigarette would be negligible according to these data: 8.7 ng per nonfilter cigarette and 1.6 ng per filter cigarette.

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* A blend of four major tobacco types: flue-cured, Burley, Oriental, and Maryland. The nonfilter cigarette dimensions were 85 mm in length, 25 mm in circumference.

Exposure from cloud-seeding operation may be significant only to a ground-based generator operator. Standler and Vonnegut (1972) estimated the concentration of silver (0.1 µm particles) in air downwind in the target area from a ground-based silver iodide cloud-seeding generator is 0.1 ng/m^3, a factor of 10^5 below the maximum allowable concentration in workplace air. At the generator site itself, however, exposure exceeds the maximum permissible concentration within 50 m downwind of the generator. Seven cloud-seeding operators with extensive exposure to silver iodide knew of no persons who had experienced any ill effects due to silver iodide, despite the fact that their hands may remain yellowed for weeks. Vonnegut,* however, recalled a technician in New Mexico in the early 1950s who claimed the aerosol from a ground-based generator aggravated his respiratory allergy, and Douglas had reported in 1970 a skin rash developing in an individual who had been within a few meters of an operating generator for 6 hours. Inhaling the acetone vapors from the unignited silver iodide solution is of more concern to some operators.

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* Bernard Vonnegut in 1947 in General Electric Laboratory experiements, showed that silver iodide crystals can initiate ice crystal formation (Fleagle, et al. 1974).

The OSHA (Occupational Safety and Health Administration) standard for silver metal and soluble compounds in the workplace air is 0.01 mg/m^3 for an 8 hr time-weighted average. Any employee's exposure in any 8 hour shift shall not exceed the 8 hr time-weighted average (39 FR 23541).

According to the American Conference of Governmental Industrial Hygienists (1977), the Threshold Limit Value-Time Weighted Average (TLV-TWA) for aerosol silver metal or soluble silver compounds as metal is 0.01 mg/m^3. The tentative value for the Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) is 0.03 mg/m^3. The TLV-TWA is based on a normal 8 hour workday or 40 hour work week, day-after-day exposure. The TLV-STEL is defined as the maximum concentration to which a worker may be exposed continuously for as long as 15 minutes without irritation, chronic or irreversible tissue changes, or sufficient narcosis to increase accident proneness, self-rescue, or work efficiency. Up to four such excursions may occur per day provided at least 60 minutes elapse between such exposures and provided the TLV-TWA was not exceeded in the time lapses.

The American Conference of Governmental Industrial Hygienists (1971) stated that, "If one assumes a 20 year exposure, a 10 m^3/day* respiratory volume, and a 50 percent body retention, a level of silver five-fold the recommended TLV[a] (0.05 mg/m^3) will result in an accumulation of 1.2 g or a probable borderline amount for the production of argyria".** The problem of how absorption of metallic silver from the lungs might parallel direct injection of silver compounds into the bloodstream was not dealt with.

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* Presumably, for the work day. Snyder, et al. (1975) estimated a 23 m^3/day respiratory volume.

** The reference is somewhat in error in stating that the gradually accumulated intake of from 1 to 5 g Ag will lead to generalized argyria. The values given by Hill and Pillsbury (1939) are 0.91 to 7.6 g, given I.V.

More pertinent information with regard to a TLV for silver in air was supplied the American Conference of Governmental Industrial Hygienists by Fassett in a personal communication (undated and unidentified as to organization). After observing silver workers for many years, he believed that silver concentrations of 0.01 mg/m^3 in workroom air are unlikely to cause argyria. Jindrichova (1962 cited) had observed 12 cases of argyria resulting from exposure to workroom air concentrations of 1 to 2 mg/m^3 in the processes of manufacturing silver varnish and its use in silvering radio-technical parts.

Winell (1975) compared the hygienic standard for chemicals in the work environment for which both the United States and the U.S.S.R. had standards. Since silver was not included, apparently the U.S.S.R. does not have a limit for silver. Argentina, Great Britain, Norway and Peru apply the U.S. standards.

Occupations where silver inhalation is still possible include silver polishers and occupations involved in melting silver or its low-melting alloys (e.g., tin-silver solder for copper plumbing). The silver nitrate manufacturers and packers were the most frequent victims of generalized argyria according to Harker and Hunter (1935), but the processes have been obsolete for decades.

Silver polisher's lung was first described in 1945. The dust inhaled contains both iron oxide (rouge) and metallic silver. The latter stained the tissued black (Aponte, 1973). Argyria was seen less often in pourers of molten silver than in silversmiths engaged in filing, soldering, polishing, engraving, etc. But, according to Lewin (1896), it was always localized rather than generalized as would occur from inhalation. Yet Koelsh (1912) (both references cited by Harker and Hunter, 1935) found that two men whose occupation involved cutting up thin sheets of silver had generalized pigmentation and suggested it was due to inhalation or ingestion of the workplace dust (300 mg silver per killigram dust).

In the melting area at the San Francisco mint on October 24 to 27, 1972, the Industrial Hygiene Services Branch of the National Institute for Occupational Safety and Health determined 0.01 to 0.04 mg/m^3 of silver fumes in the air (average 0.02 mg/m^3; the threshold limit value of 0.01 mg/m^3 was exceeded in seven of the eight samples). The melting and casting operations caused smoke and fumes throughout the melting room despite adequate ventilation over the melting area (Anania and Seta, 1973). Although silver is seldom encountered in new U.S. coinage except for the special silver-containing editions of U.S. Eisenhower dollars made only at the San Francisco mint from time to time, such information is probably applicable to the extent of occupational exposure at firms that make medallions, silver bars, and other commemorative items of cast silver. Sterling silverware and holloware are generally manufactured without melting operations. Silver platers are more at risk to cyanide poisoning than to silver.

Dermal

Laws in many states still require that a few drops of a 1 or 2 percent silver nitrate solution be applid to the conjunctiva of the eyes of newborn infants to prevent ophthalmia neonatorum by transmittal of gonorrhea from the mother (Martin, 1965). Use of silver nitrate is a legal requirement in Denmark, but it is not used in Japan or Australia. Elsewhere there is a free choice between silver nitrate and antibiotics. Silver nitrate is no longer used in 20 percent of U.S. hospitals because of the dangers of chemical conjunctivitis (Shaw, 1977).

In the U.S., several silver-containing pharmaceuticals for use on skin or mucous membranes can be obtained; some do not need a prescription. Among the medications are Argyrol^R (mild silver protein) and Protargol^R (strong silver protein), Neo-Silvol^R (colloidal silver iodide in a gelatin base), silver nitrate, and Silvadene^R (silver sulfudiazine) (Pariser, 1978).

The risk of argyria from silver-containing topical medicinals continues today. Marshall and Schneider (1977) reported a case of systemic argyria in a 46 year-old woman which had first begun to appear by November, 1971. She had begun using silver-nitrate applicators for bleeding gums from ill-fitting dentures, upon the advice of her dentist. From April, 1970, she had used three applicators per week and continued using them even after the first bluish discoloration appeared about her nose and forehead. By July, 1972, she was already strikingly pigmented, was diagnosed as having argyria, and was advised to discontinue use of the applicators. In 1973, the pigmentation of her abdominal organs was noted during an exploratory laparotomy. None of the patient's physical ailments were attributed to the use of silver nitrate.

Moyer and his associates instituted the use of hypotonic silver nitrate burn treatment in April, 1964, at Barnes Hospital in St. Louis, Missouri. It was discontinued there in December, 1967. Monafo had developed colloidal silver isotonic solutions, and Margraf and Butcher had developed other silver salts in ointment. In the opinion of Monafo and Moyer (1968) of St. John's Mercy Hospital in St. Louis, "Because most salts of silver, other than the nitrate, are insoluble..., it was predicted that due to precipitation at the wound surface, little or no absorption of silver would occur through burn wounds. It was therefore anticipated that systemic toxicity would be inconsequential. Moreover, argyria, the slate-gray discoloration of the skin that results from the ingestion or absorption of silver is innocuous physiologically and does not shorten life." No patient had developed argyria, but silver was detected in plasma and urine. Patients with extensive burns treated for up to 80 days had 0.05 to 0.30 mg silver per liter in their plasma.

Hartford and Ziffren (1972) reported on the results of 0.5 percent silver nitrate use on the dressings of 220 burn patients. Compared with the rate in the 1950-1960 decade, mortality had been dramatically reduced. By the late 1960s, the search for a less soluble, but effective silver compound lead to the synthesis (by C. L. Fox, Jr.) and clinical trials of silver sulfadiazine.

Side effects, not due to the silver content, are described in the "Effects" section. Absorption obviously can occur since silver was frequently found in the urine when silver nitrate was used.

Silver sulfadiazine by 1974, according to Fox (1975), had been used in the treatment of more than 10,000 burn patients in many countries for more than 7 years. It had been approved by the regulatory agencies in the United States and the United Kingdom so that more general use had begun.

Less than 10 percent of the sulfadiazine is absorbed, and far less of the silver. Daily treatment of 1 m^2 of burn surface (a 50 percent burn in an adult) requires 200 g $AgNO_3$ (127 g Ag) (40 liters of 0.5 percent solution) or 4 g silver sulfadiazine (1.2 g Ag) (one 400 g jar of 1 percent cream or lotion). Fewer than 10 of 10,000 patients showed any drug sensitivity (Fox, 1975).

A 1 percent silver cream made of silver nitrate, zinc sulfate, and allantoin has been developed for self-care treatment of cutaneous ulcers. In a study of 400 chronic skin ulcers in 264 patients, 84.5 percent were completely healed with 3 to 40 weeks (10 weeks average) (The Silver Institute, 1977c). The compound is another slow-release form of silver, and is less likely to produce argyria than silver nitrate preparations alone.

Silver nitrate hair dyes have been used regularly since about 1800. Sodium thiosulfate developers are added to the hair first followed by 0.5 to 15 percent silver nitrate solutions containing various amounts of ammonia to give gradations of shade. The 5 percent solution with ammonia is widely used to dye eyebrows and eyelashes and is the only colorant commonly used for the purpose in the U.S (Wall, 1957 and 1972). At least one case of argyrosis has been reported from such use. An Italian physician who dyed his eyebrows, moustache, beard and eyelashes with a silver dye for 25 years developed argyria in the conjunctiva of both eyes (Wall, 1957).

Several swimming pools in the U.S are equipped with filtering systems of activated carbon of very high surface area coated with pure metallic silver. The effective water concentrations of silver ions are 20 to 40 µg/liter (The Silver Institute, 1973a, 1973c, 1974, and 1976c). Dermal absorption of silver from swimming pools is not expected, although absorption through the conjunctiva is possible. Although evidence is cited in Part II.A. that mucous membranes and wounds allow absorption of silver compounds to an unknown extent,* very little, if any, ionic silver is absorbed by intact skin.

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* That is, the percent of the total dose absorbed has not been calculated; however, long-term use of the topical silver medicinals (generally silver nitrate) for mucous membranes has certainly led to argyria.

PHARMACOKINETICS

Absorption

Silver may enter the body via the respiratory tract, the gastrointestinal tract, mucous membranes, or broken skin. Some reports even claim absorption through intact skin. In most cases of argyria, caused by occupational exposure, absorption has been via the respiratory tract or the conjunctiva (Hill and Pillsbury, 1939). Up to 10 percent of a single oral dose of silver is absorbed. The literature data do not lend themselves to a ready calculation of the degree of absorption after inhalation or dermal exposure. Absorption from even nonintact skin appears to be much less than 1 percent.

Rats ingesting 1.68 g/kg of colloidal silver for 4 days or 0.42 g/kg for 12 days showed higher silver concentrations in the lungs than in the liver. Based on distribution studies described in Part II.B. below, the amount found in the lungs is so high that perhaps the rats aspirated part of the dose. Otherwise, the total amount of silver recovered in the heart, lungs, kidney, spleen, liver, and muscles would indicate that at least 2 percent of the higher dose (if one assumed the average rat weighed 200 g) was absorbed. Apparently, almost 5 percent of the silver was absorbed at the lower dose (Dequidt, et al. 1974).

Scott and Hamilton (1950) concluded that rats absorbed 0.1 percent of a carrier-free dose of radiosilver upon ingestion.* Rats were given the doses intragastrically. Four days after the dosing, 99.0 percent of the original dose had been eliminated in the feces and 0.18 percent in the urine; yet the tissue distribution apparently totals 0.835 percent; 0.52 percent in the lungs, 0.025 percent in the blood, 0.11 percent in the G.I. tract, 0.034 percent in the skin, and 0.076 percent was in the balance remaining after the other internal organs, bones, and muscles revealed no silver.

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* Furchner, et al. (1966b) state that the findings of the Scott and Hamilton report indicate about 4 percent absorption from the gastrointestinal (G.I.) tract. They found that mice absorbed less than 1 percent.

Dogs (4 male beagles, average 5.5 years, 12 to 16 kg) were presumed to absorb 10 percent of oral doses of 0.6 μCi ^{110}Ag as the nitrate since only 90 percent was lost very rapidly (Furchner, et al. 1966b).

Rabbits (3) inhaled a 10 percent colloidal silver solution for 8 hr (Kohdradova, 1968a and 1968b) and were immediately sacrificed. In the tracheal epithelium, silver had accumulated in the large vacuoles in the cytoplasm of epithelial cells.

In a human who had accidentally inhaled ^{110m}Ag, most of the inhaled silver had a biological half-life of about 1 day, probably due to rapid mucociliary clearance, swallowing, and fecal excretion. By whole-body counting on the second day, silver activity was seen in the liver, which indicated some absorption although the published data do not permit a calculation of absorption (Newton and Holmes, 1966). Newton and Holmes believed colloidal forms of silver are the species of silver absorbed in the lungs and that phagocytosis would account for the localization in the liver. They cited a study by Hahn and Corrothers (1953) in which the radiosilver coating of colloidal gold particles administered intrabronchially to dogs was gradually leached off in the lungs and appeared in the liver.

West, et al. (1950) reviewed early investigations into cutaneous absorption of silver: Muller, in a privately printed 1936 report cited in Hill and Pillsbury (1939), stated that all of the silver oxide in a 5 percent oily dispersion was absorbed after topical application to intact skin, wounds, or mucous membranes. He found no silver deposits in the skin or underlying tissue, but he claimed to have accounted for 73.1 to 88.5 percent of the silver administered to four guinea pigs in their excreta withing 31 days of the inunction of their intact skin. Win (1887) could find no permanent deposit of silver granules 6 weeks after their dermal injection. Jacobi (1878) could not produce generalized argyria, however, by S.C. injections of a silver solution in rabbits; yet Pincussen and Roman (1931) found silver in blood, skin, kidney, spleen, and liver after S.C. injection of silver sulfate in rats. West, et al. (1950) citing unpublished data of West, Elliott, and Hahn, found activity in many organs and feces of albino rats after S.C. injections of a mixture of ^{108}Ag and ^{110}Ag.

Hill and Pillsbury (1939) reviewed several studies in which silver was apparently not absorbed from intact skin. The Muller study was described in a footnote.

The depilated backs of rats were painted daily with a saturated solution of Collargol (colloidal silver and silver oxide) for 3 months. By atomic absorption spectrometry and colorimetry, traces of silver were found in the heart and lungs, 1.54 mg/kg in the kidney, 1.50 mg/kg in the spleen, and 0.16 mg/kg in the liver (Dequidt, et al. 1974).

Wahlberg (1965) determined that the absorption of silver nitrate from a solution containing 25.8 g Ag/liter by the intact skin (3.1 cm^2) of guinea pigs was less than 1 percent 5 hours after topical application.

Argyria following use of silver preparations as topical applications to the mucous membranes was relatively common according to Hill and Pillsbury (1939), but the argyria was usually described as "local" rather than "generalized," which would indicate systemic absorption.

Marshall and Schneider (1977), however, have described a rare, present-day case of generalized argyria due to assiduous use of a silver nitrate stick for bleeding gums due to ill-fitting dentures.

Applications of silver nitrate dressings to open wounds allows systemic absorption of silver. Constable, et al. (1967) treated open wounds (3.5 x 3.5 cm^2) on the backs of guinea pigs with 0.5 percent $AgNO_3$ solution for 5 days. In Table 6, the range of silver concentrations in the organs of four or five topically treated guinea pigs are compared with those in one guinea pig drinking the 0.5 percent $AgNO_3$ solution (probably not the same amount as received by topical treatments). Loss of silver from the liver was fairly rapid after cessation of treatments. After 1 week, $<$40 percent remained; after 2 weeks, $<$ 25 percent. Since the $AgNO_3$ contained some ^{111}Ag (t-1/2 = 7 days), radioautographs showed that silver was concentrated in the Kupffer cells and around the bile canaliculi with very small amounts in the glomeruli and most in the kidney in the cells lining the renal tubules.

TABLE 6

Comparison of Tissue Distribution after Dermal Gastro-Intestinal Absorption of Silver from a 0.5 Percent $AgNO_3$ Solution

Organ	Concentration, mg/kg	
	Dermal Route	Gastrointestinal Route
Skin	3.0-35.5	1.5
Skin by wound	42.5-3,491.1	-
Ulcer	2.0-6,649.5	-
Liver	15.2-29.6	35.3
Bile	0.5-1.8	0
Kidney	7.6-152.0	2.1
Lymph node	1.8 to 14.4	2.8
Stomach	2.2 to 24.9	164.8
Intestine	3.8 to 38.0	10.0

Bader (1966) analyzed the organs of two burn patients who had been treated with fresh dressings of silver nitrate continuously for at least 6 days or for every 8 hours for 30 days. In the 66 year-old man, who had died of a brain tumor about 50 days after the 8-hr treatment was initiated, the silver concentrations in the tissues were slightly above normal: bone, 0.025 mg/kg; heart, 0.040 mg/kg; kidney, 0.140 mg/kg; and skin, 2,800 mg/kg. The second patient was an 18 year-old male, who died of respiratory complications on his 7th hospital day. Before death, the silver concentration in his urine was 0.038 mg/liter and in his blood, 0.12 mg/liter. There was no silver detected in his lungs or brain; but the concentrations in other tissues were: heart, 0.032 mg/kg; kidney, 0.14 mg/kg; spleen, 0.23 mg/kg; liver, 0.44 mg/kg; muscle, 2.0 mg/kg; and skin, 1,250.0 mg/kg. On the basis of information of Fox (1975), the daily dose of silver from silver nitrate dressings is 127 g. The patient dying on the 7th day was probably treated for at least 6 days, receiving 762 g silver. On the assumption that his body weight and the weight of his organs were those of Reference Man (Snyder, et al. 1975) and with the exclusion of the silver content of his skin, one can calculate that the organs named contained 57.5 mg silver. Because the silver concentration of his liver and heart were approximately the same as those of the older man, we will assume that his bones had the same silver content, 0.9 mg. These values plus his urinary output for at least 1 day, certainly no more than 0.04 mg and probably less because of possible renal impairment, total 58.44 mg or 0.008 percent of the 762 g dose of silver.

Silver sulfadiazine has very low water solubility and probably remains in the wound exudate according to Nesbitt and Sandman (1977). The solubility in distilled water cannot be detected by any potentiometric method. At pH 3.851 with a nitric acid buffer, ionic strength 0.1 M, the solubility of Ag+ was about 6.5 x 10^{-5} M; at pH 2.128, about 60 x 10^{-5} M. Yet, Wysor (1975a) citing a Marion Laboratories brochure on Silvadene dated March 1, 1972, stated that very large concentrations of silver sulfadiazine applied topically has caused silver deposition in the kidney basement membrane. Wysor (1975a) gave CF-1 mice infected with Plasmodium berghei (oral) doses of 1,050 mg/kg of various silver sulfonamides for 5 days. Only silver sulfadiazine proved effective in curing the mice of their malaria, presumably, it was solubilized and absorbed.

Dermal absorption of silver sulfadiazine from wounds is low. In clinical trials with silver sulfadiazine cream, Fox, et al. (1969) reported that when 5 to 10 g of the drug was applied to the burned surface of 31 patients, the levels of sulfadiazine in the blood were 10 to 20 mg/liter and there was 60 to 300 mg/liter in the urine (24-hr excretion of 100 to 200 mg). When burned guinea pigs were treated with radioactive silver sulfadiazine, Fox, et al. (1974) did not detect any radioactivity in the organs or blood.

Moncrief (1974) reported that 10 percent of the sulfadiazine of silver sulfadiazine burn-wound applications is absorbed to give blood levels of 15 to 40 mg/liter, peaking 3 to 4 days after initiation of treatment. The daily absorption rate decreases during the first 10 to 15 days after the initiation of therapy. Radiosilver does not appear in the blood from silver sulfadiazine; but when silver nitrate

TABLE 7

Silver Concentrations in Human Blood and Excreta
(mg/kg)

Subject	Blood	Urine	Feces
Patient with 70 percent burns, treated with silver sulfadiazine for 1 month	0.75	0.73	3.2
Same patient, 2 months later, after grafting	0.13	0.12	19.3
Patient with 60 percent burns, treated with silver sulfadiazine for 3 months, off treatment for 1 month	0.09	0.02	1.0
Control adult	0.05	0.003	0.53
Child with 15 percent burns, 11-months-old (length of silver treatment not given)	-	7.0	6.0
Control child	-	2.0	0.21

soaks are used, there is 0.05 to 0.3 mg/liter silver in the plasma.

Burke (1973) compared the excretion of silver by children and adults, untreated and treated with silver sulfadiazine. His results are in Table 7.

Distribution

The amount of silver, its chemical form, and the route by which it is administered affect the tissue content and distribution of silver within the body (Furchner, et al. 1968). It is retained by all body tissues. The primary sites of deposition in persons who have never taken silver therapeutically are the liver, skin, adrenals, lungs, muscle, pancreas, kidney, heart, and spleen. Silver is also deposited in blood vessel walls, testes, pituitary, nasal mucous membrane, maxillary antra, trachea, and bronchi (Sax, 1963). Although silver does not accumulate in the lungs with age, it was present in 39 percent of the lungs from Americans analyzed by Tipton and Cook (1963). Examinations of accidental death victims indicated that the silver content of the myocardium, aorta, and pancreas tended to decrease with age (Bala, et al. 1969). Silver accumulates in the body with age, however, even if none is administered intentionally (Hill and Pillsbury, 1939).

A striking feature of argyria is the regular deposition of silver in blood vessels and connective tissue, especially around the face, conjunctiva, hands, and fingernails (Hill and Pillsbury, 1939). The silverbearing particles in one case of localized argyria of a photoprocessor were found to be silver sulfide (Ag_2S), possibly contained in the mitochondria (Buckley, et al. 1965). The silver-containing particles were sparsely distributed at the dermo-epidermal junction of the papillary bodies adjacent to the epidermal portion of the sweat ducts. The silver had entered the skin via the sweat glands (Buckley, 1963).

In argyria, aside from the blood vessels and connective tissues, the dermis of the skin, glomeruli of the kidney, choroid plexus, mesenteric glands, and thyroid contain the greatest amounts of deposited silver. The epithelium is free of silver deposits (but Buckley, et al. 1965, report that silver ions are present there).* Other tissues where deposition may occur include: bone marrow, pancreas, liver, spleen, testes, and ovaries (Hill and Pillsbury, 1939; Sax, 1963; Van Campen, 1966). The adrenals, lungs, dura mater, bones, cartilage, muscles, and nervous tissue are minimally or never involved as deposition sites for silver (Hill and Pillsbury, 1939). Exposed skin shows greater amounts of melanin in the dermis and epidermis. Robert and Zurcher (1950, cited by Lever, 1961), had stated that silver favors melanin formation by increasing oxidative processes. Silver is especially deposited in intima of blood vessels and connective tissue of internal organs. Basement membranes around the acini of the testes and of the choroid plexis are rich in silver granules (Harker and Hunter, 1935).

* According to Lever (1961) in the 3rd edition of Histopathology of the Skin, in argyria, silver is found in the dermis--chiefly outside the cells, as uniformly sized particles ("...fine, small round, brownish...")--but never the epidermis. The particles, lying singly or in clumps, are $< 1\mu$ in diameter. "Under a dark-field microscope, the silver appears as brilliantly refractile, white granules against a dark background." Melanin and hemosiderin granules are larger, largely intracellular, and nonrefractile on dark-field illumination.

Polachek, et al. (1960) reported the metabolism of radiosilver in a patient with malignant carcinoid that agreed reasonably well with the carrier-free silver rat studies of Scott and Hamilton (1950). The radiosilver was incubated with the patient's own blood and was first associated most with the erythrocytes and the globulin fraction of the plasma (77 percent in the globulin, 15 percent in the albumin, and 8 percent in the fibrinogen fractions). Upon injection (I.V.) into the patient (with 0.002 mg carrier Ag/kg), the 43 μCi radiosilver was removed rapidly from the blood, presumably by the liver with biologic half-life of 48 days. At 7 minutes after injection, only 30 percent of the injected dose remained in the blood; at 2 hours, 10 percent remained; and at 1 to 20 days, 2 percent. Urinary excretion was 5 percent of fecal excretion. Excretion was much slower than in the rat studies. Only 0.5 to 3 percent of the original dose was eliminated in each of seven 24-hour periods in the first 21 days post-administration. Urinary excretion in these 24-hour periods ranged from 0.03 to 0.29 percent.

The patient lived 195 days after the injection. Analysis of the organs post mortem showed the highest concentrations (counts per minute per gram) in: liver, 70.0; skin, 37.7*; kidney (left), 10.0; brain, 9.2; and kidney (right), 7.5. From 4.0 to 5.6 cpm/g was found in an abdominal lymph node, an adrenal gland, the primary carcinoid in the ileum, a testis, the aorta, and the pancreas; and 2.2 to 3.8 cpm/g was found in the urinary bladder, prostate, heart, stomach, rib, and ileum. Smaller concentrations were found in the carcinoid in the liver (metastatic), a lung, muscle, and the spleen (Polachek, et al. 1960).

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* Because of its relative weight, the skin had the highest accumulation of silver.

Intramuscular injections of dextrin-protected radiosilver colloid left much material at the injection site, but an I.V. dose in albino rats (1 ml contained 1.72×10^6 cpm) was mainly found in the reticuloendothelial system. The bone content was primarily in the marrow. The continued presence of activity in the blood suggested that tissue-deposited silver was being translocated. A gelatin-protected silver colloid injected I.V. into albino mice was also deposited in highest concentrations in the reticulondothelial system; 22 hours after I.P. injection of the gelatin-protected silver colloid into 5 albino mice, 36.5 percent of the activity was in the gastrointestinal tract and contents; 16.5 percent in the liver; 10.2 percent, in muscle; 3.5 percent, in bone; and 0.4 percent, in the skin (except the head) (Gammill, et al. 1950).

Table 8 adapted from Smith and Carson (1977) reviews some other animal data on early distribution of injected silver compounds.

Deposition of carrier-free radiosilver in rats was similar after I.M. and I.V. injections. The most interesting information from the studies of Scott and Hamilton (1950) was the distinct difference in organ accumulation between carrier-free amounts and doses containing added stable silver compound as carrier. Table 9 shows the difference in distribution at Day 6 post I.M. injection when three rats per group were given carrier-free silver or radiosilver with 0.1 mg stable silver (0.4 mg/kg), or with 1.0 mg stable silver (4.0 mg/kg).

Obviously, the liver had difficulty maintaining its efficient removal of silver at a dose of 0.1 mg/rat, but the dose of 1.0 mg/rat definitely showed the limitation

TABLE 8

Silver Distribution in Animal Tissues

Organism	Organ	Form of Ag	Distribution at 10 min	30 min	1 hr	3 hr	6 hr	24 hr	2 days	7 days	Dosage	Remarks	Reference
White mice	Blood	$^{110}Ag^{125}I$	19.7%		13.5%	15.2%	0	0	0	0	0.2 ml i.v. of 50-60 µg/ml in tail vein	Ag also found in lungs, kidneys, small intestine, intestine, bladder, muscle, testes, and brain.	Anghileri (1969)
	Liver		65.6%		48.3%	40.7%	44.3%	30.9%	20.0	10.11%			
	Spleen		0.35%		0.70%	0.60%	0	0	0	0			
	Stomach		0.51%		0.92%	1.25%	0	0	0	0			
	Thyroid		0		0.02%	0	0	0	0	0			
	Bone		0.42%		0.31%	0.51%	0.93%	0.01%	0	0			
		Total	86.58%		63.75%	58.32%	45.25%	30.91%	20.0	10.11%			
White mice	Blood	$^{110}Ag^{82}Br$		0.82%	1.12%			0.56%			0.2 ml i.v. of 50-60 µg/ml in tail vein	Results indicate Ag is released in an insoluble form and not as Ag^+ Radiosilver is slowly excreted through bile and urine.	Anghileri (1969)
	Liver			58.7%	63.6%			26.1%					
	Spleen			0.34%	0.18%			2.09%					
	Stomach			0.73%	0.57%			0.41%					
	Thyroid			-	-			-					
	Bone			0.21%	0.14%			0.45%					
		Total		60.80%	63.61%			23.61%					
						2 hr							
Rats	Lungs	$^{110}AgNo_3$ at pH 5.0 in 0.05 M acetate buffer				Found							Anghileri (1969)
	Kidneys					Found							
	Heart					Found							
	Pancreas					Found							
	Small intestine					Found							
	Large intestine					Found							
	Bladder					Found							
	Muscles					Found							
	Testes					Found							
	Brain					Found							
Rats	Blood	$AgNO_3$ and $^{64}Cu(NO_3)_2$ injected into in vivo ligated segments of the G.I. tract.									0.01 umoles Cu^{2+} in 0.4 ml distd. H_2O with 1.5, 3.0, and 6.0 umoles Ag^+	Ag had little effect on uptake of Cu except that a significantly greater proportion of Cu was deposited in the liver and significantly less retained by the blood in Ag-treated rats.	VanCampen (1966)
	Heart												
	Kidneys												
	Liver												
	Spleen												

TABLE 9

Distribution of Silver in the Rat at Day 6 Following Intramuscular Injections of Different Doses of Silver (percent of dose per organ)

	Dose		
	Carrier-Free	0.1 mg	1.0 mg
Percent of Dose Absorbed	92.1	63.7	53.5
Absorbed			
Heart and lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.50	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
G.I. tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33
Unabsorbed	7.9	36.3	46.5

of its capacity so that the rest of the reticuloendothelial system had to handle much more silver. At the highest dose compared with the carrier-free dose, the liver had accumulated 94 times as much of the absorbed dose of silver; the spleen, 269 times as much; and the skin, 31 times as much. Other organs, including the kidney, had about 10 times as much silver. Scott and Hamilton presumed that a dose of 5 mg silver per killigram I.M. would be required to give a tissue distribution similar to that seen in classical argyria.

West, et al. (1949), cited in later papers and West, et al. (1950) had shown that ^{111}Ag nitrate when injected I.M. or I.V. "...is taken up by blood leukocytes and carried into inflammatory body areas."* Presumably, the Ag-protein complexes formed were phagocytized. Since insoluble silver compounds would be less corrosive and also phagocytized, West and Goldie (1956), injected normal and tumor-bearing mice with $^{111}Ag_2O$ to see the distribution of the radioactivity by autoradiographs. In normal Swiss albino mice given S.C. injections of 0.1 or 0.2 mCi $^{111}Ag_2O$, the activity 24 hours after the injection remained mostly at the injection site with a large fraction in the liver and minor amounts in the spleen, stomach, colon, kidney, and lung. In normal mice given the injections I.P., most of the activity was in the liver; some remained at the injection site, but absorption was much higher than by S.C. injection.

* West, et al. (1950) found that up to 10 percent of intradermal injections of labeled silver nitrate ($^{108,110}Ag$) remained at the injection site after 72 hours. When Staphylococcus aureus was injected simultaneously in the same leg five times as much silver was then found at the injection site after 72 hours. But if injected in different legs, the activity was preferentially found at the site of bacterial injection.

Thus, higher activity was seen in each of the organs than with S.C. injections. However, mice with tumors (Sarcoma 180, Sarcome McGhee, Carcinoma C_3H/BA, and Carcinoma EO771) showed by far the major activity in the tumors and intracavity exudates when injected with radiosilver near the tumor site (S.C. into the tumor periphery, into the pleural cavity with malignant growth, or into the peritoneal cavity bearing malignant growth). West and Goldie (1956) explained the preferential silver absorption by tumors as follos: a S.C. injection in normal mice remained largely at the injection site, presumably clogging the lymphatics. When adjacent tumors were present, they apparently absorbed the $^{111}Ag_2O$ into macrophages and interspaces of malignant tissue.

In argyric rats given 0.5 percent silver nitrate in their drinking water for 9 months, silver was especially found in lysosomes of the liver's Kupffer cells, at the basal membrane of the capillaries, and the connective tissue cells of the pancreas. In the parenchymatous cells, Putzke (1967) found silver only as a lipoid-silver complex or in lipofuchsin-like lysosomes and in residual bodies. The lysosomes were thought to be responsible for intracellular transport and the extrusion of silver. In the liver, there was increased activity of cytochrome oxidase, but marked decrease in the activity of succinate dehydrogenase.

Ham and Tange (1972) cited numerous studies wherein silver nitrate was administered in the drinking water of rats to study glomerular basement membrane formation. These authors gave drinking water containing 2,500 mg/liter $AgNO_3$ for 12 weeks to albino and hooded female rats, killing pairs of animals at 1 to 12 weeks to study the tissues by light and electron microscopy. Other pairs of animals were killed at 1 to 10 months after silver intake. Four of each strain were also killed for study 16 months after the cessation of silver intake. As shown in Table 10 the silver content in the liver was similar in both strains, but varied by strain and individuals of the same strain in the kidneys. Abnormalities in glomerular epithelial and endothelial cells were not progressive or consistent. Bloom, et al. (1959) cited by Ham and Tange (1972) in observing the phenomenon of increased formation of basement membrane thought the increase might be greater than normal thickening due to aging.

Moffat and Creasey (1972) fed ten adult rats and three adult rabbits drinking water containing 1,500 mg/liter $AgNO_3$ for 4 to 20 weeks to study the permeability of medullary vessels of the kidney to protein. Only the rat kidney showed heavy silver deposits in the glomeruli and outer medulla basement membranes. Both species had heavy deposits in the inner medulla, but the distribution differed markedly. In the rat, most of the silver was in the basement membrane of the vessels and loops of Henle, but the heaviest deposits were around the descending vasa recta. The main deposits in the rabbits were also in the vessels and loops of Henle, but the distribution in each vessel or loop was asymmetrical. The most silver lay on the side adjacent to the collecting duct. In the silver-dosed rats, the occurrence of kidney cells that were degenerating was more common than in normal rats.

Creasey and Moffat (1973) also cited several studies in which silver nitrate had been administered in drinking water to experimental animals to study the basement membranes of some (brain, eye, and renal glomeruli) of the many kinds

TABLE 10

Silver in Formalin-Fixed Rat Tissues After Drinking Silver-Containing Water, mg/kg*

(Ham and Tange, 1972)

	Hooded Rats		Albino Rats	
	Liver	Kidney	Liver	Kidney
3 Months' intake of silver at 2,500 mg/liter in drinking water	6.8, 7.0	6.1, 9.8	6.3, 7.0	3.7, 7.1
10 Months after removal of silver from drinking water	1.4, 2.8	3.7, 4.3	2.2, 2.5	1.8, 3.4
16 Months after removal of silver from drinking water	0.8-1.4	2.7-4.1	0.7-1.6	3.0-6.0

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* Determined by potentiometric titration.

of tissues in which silver accumulates. Silver is carried in the blood as a silver-protein complex, and its deposition in tissues appears to indicate vascular permeability to protein. Extravasation of protein in the kidneys occurs in immature rats (younger than 3 months) much less than in adults; and this was borne out by the slower rate of appearance (12 to 14 weeks versus 5 weeks) and finer particulate size ($<$30 nm versus 30 to 90 nm) of silver granules deposited in the kidneys of immature rats given 1,500 mg/liter $AgNO_3$ solution for 4 to 15 weeks after weaning, compared with adults on the same regimen. The increasing amount of silver deposited in the rat kidney glomeruli with age has also been attributed to increasing glomerular filtration rate.

Silver granules were detected by electron microscopy in the glomerular basement membrane of random-bred adult mice after 12 days of ingesting drinking water containing 6 m$\underline{M}$ $AgNO_3$ (648 mg/liter Ag). After 14 weeks of silver ingestion, larger aggregates were observed in the basement membrane and mesangium. Within 21 weeks after cessation of silver ingestion, the silver deposits did not change significantly (Day, et al. 1976). Some of the mice were used in a study of immune complex glomerular disease induced by I.P. injections of bovine serum albumin. The silver-labelled basement membrane helped determine that the immune deposits were on the intracapillary aspect of the basement membrane (Hunt, et al. 1976).

Metabolism

Silver is transported in the protein fractions of the plasma, especially the globulins. The reticuloendothelial system, especially the liver, handles most of the removal of absorbed silver from the body at moderate doses (0.4 mg/kg in rats, according to Scott and Hamilton, 1950). At higher doses, deposits are markedly increased in the skin. Inhaled silver particles that are not removed from the lungs by the mucociliary reflex and coughing are probably phagocytized and ultimately removed to the liver, from which they are eventually excreted via the bile. Formation of silver selenide deposits in the liver may well be another method of detoxifying silver (the interactions of silver and selenium are discussed under "Synergism and/or Antagonism". Many studies have focused on elucidating the chemical forms of the silver deposits in the skin. The most probable forms are metallic silver, silver sulfide, or silver complexes with sulfur amino acids of proteins. Since they are so inert, they cannot be removed by common heavy metal detoxification procedures. These deposits appear to be another method of detoxification by the organism. In the kidney, complexation with metallothionein may be another detoxification pathway.

Transport of silver in the blood is largely in the globulin fraction. None of the silver content of blood is dialyzable "to any extent" through cellophane (Scott and Hamilton, 1948). In vitro, the distribution of carrier-free ^{105}Ag after 3 days in heparinized rats' blood containing an equal volume of isotonic saline was: hemoglobin, 8.4 percent; ghosts of the cells, 11.6 percent; globulin, 64 percent; albumin, 16 percent; and the protein-free fraction, 0.001 percent. In vivo, the distribution of total amount of radiosilver activity in rats' blood 5 minutes after I.V. injection was erythrocytes, 10.2 percent; globulin, 57 percent; albumin, 32 percent; and the protein-free fraction, 0.7 percent. (The liver already contained 86 percent of the injected dose by 5 minutes) (Scott and Hamilton, 1950).

Lifshits (1965) reported the distribution of endogenous silver in the blood of 16 healthy humans (in milligrams per liter whole blood). In the plasma, the fibrinogen fraction contained 0.0018 mg/liter; the globulins, 0.0064 mg/liter; the albumins, 0.0024 mg/liter; and minerals, 0.0014 mg/liter. In the erythrocytes, the silver distribution was stroma, 0.0038 mg/liter; nonhemoglobin proteins, 0.0009 mg/liter; and erythrocyte minerals, 0.

Silver iodide is readily broken down by biological tissues. Anghileri (1968) injected 0.2 ml of $Ag^{131}I$ (0.23 mg AgI/ml and 10 μCi ^{131}I/ml) into the tail veins of young albino mice (15 to 20 g). In a similar experiment, the silver portion of the molecule was labeled (^{110}Ag). Less radioactivity was observed in the liver with ^{110}AgI than with $Ag^{131}I$ (53 percent versus 70 percent of the injected dose after 10 min), but the ^{110}Ag radioactivity remained longer in the liver (21 percent versus 4.1 percent at 24 hours). The distribution of radioactivity was much higher in the stomach and thyroid with ^{131}I than with ^{110}Ag in the injected silver iodide during the first 24 hours.

Camner, et al. (1974) reported that silver-coated 5 um Teflon^{R}* particles were phagocytized _in vitro_ by rabbit alveolar macrophages in the presence of serum more slowly than were similar particles coated with aluminum or chromium and at about the same rate as were particles coated with manganese or uranium. When serum was not added, there was less difference in phagocytization rates. The former case is more comparable with the in vivo situation. (For silver, the average number of particles phagocytized per macrophage in the presence of serum after 1.5 hours was 0.58; for aluminum, 0.72. Without serum, the numbers were 0.38 and 0.40, respectively.) There were fewer than 4 percent nonviable macrophages after the 1.5-hour exposure of a monolayer of macrophages from disease-free rabbits to the particle suspension in 75 percent Parker 199 solution and 25 percent autologous rabbit serum or in 100 percent Parker 199 solution.

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* Registered trademark of E.I. duPont de Nemours and Company, Inc., Wilmington, Delaware.

After daily applications of 1 percent silver sulfadiazine cream to the abraded skin of albino rabbits for 100 days at dosages of 5.0, 10.0, or 15.0 g/kg/day, the kidney tissues were treated with various solvents* in an effort to determine the chemical form of the silver deposit. Sulfadiazine was not detected in chloroform extracts of acidified tissue homogenates.** Since only the strongly oxidizing solvent 16M nitric acid dissolved any of the kidney tissue silver deposits (the range of silver concentrations in four rabbit kidneys by atomic absorption spectrometry was 172.3 to 247.0 mg/kg), Grabowski and Haney (1972) concluded that the form of silver was as a silver tissue complex whose dissociation under normal conditions would be minimal, and whose only physiological threat would be mechanical interference to kidney function. No structural damage or impairment had been noted in the kidneys, however.

* 16M HNO_3, 30 percent NH_4OH, 50 percent CH_3CO_2H, 9.0 percent H_2NCSNH_2, 37.5 percent HCl.

** It is not surprising. The sulfadiazine probably remained in the acid solution as a salt: $A^- \; {}^+NH_3C_6H_5SO_2NHC_4N_2H_3$.

Pariser (1978), using the differential solubility methods*** of Buckley, et al. (1965), found that only cyanide solutions removed the silver from tissue sections of argyric patients (ages 83, 58, and "elderly"). This suggested that the chemical form of silver was as silver sulfide or some other highly insoluble complex rather than metallic silver.

Chromatographically purified metallothionein from normal rat liver contained significant concentrations (by neutron activation analysis) of Cd, Zn, Cu, Hg, and Ag. Experiments with ^{110m}Ag$^+$ showed further incorporation into metallothionein (Sabbioni and Girardi, 1977). Possibly this is the mechanism whereby the kidneys excrete bound silver.

*** Tissues were extracted with thiosulfate fixing bath (dissolves silver mercaptides, oxides, chlorides, bromides, iodides, carbonates, and phosphates); ferricyanide-bromide bleach followed by thiosulfate fixing bath (dissolves metallic silver); and 5 percent sodium cyanide (which dissolves most insoluble silver salts such as silver sulfide).

Excretion

Regardless of route and chemical form administered, fecal excretion of silver always predominates over urinary excretion. Most absorbed silver is excreted into the intestines by the liver via the bile.

Scott and Hamilton (1950) showed that the liver is the chief organ responsible for elimination of absorbed silver. The silver content in the liver, feces, and gastrointestinal tract contents was reduced when bile duct ligation or light chloroform anesthesia (produces liver damage) in rats was performed prior to injection of carrier-free radiosilver. Ordinarily, after I.M. injection of 1 μCi radiosilver (0.1 μg), 60.9 percent of that absorbed was excreted in the feces on the first day, and 21.4 percent was already in the gastrointestinal tract. After bile duct ligation, on day 2, 57.6 percent of the activity still remained in the liver, 5.06 percent was in the G.I. tract, and only 6.85 percent was in the feces. After light chloroform anesthesia for 3 hours, the rats excreted silver at 0.0001 the normal rate.

Urinary excretion of silver is generally very low. At 4 days after an I.V. dose of radiosilver, rats had excreted 94.06 percent of the dose in the feces and 0.34 percent in the urine; at 16 days, 97.8 percent and 1.8 percent respectively (Scott and Hamilton, 1950). Administratin of Ca EDTA, a common metal chelating agent, reportedly increased urinary excretion of silver. Ligating the bile duct in laboratory animals increased renal excretion while reducing fecal excretion by a factor of 10, thereby further demonstrating the biliary nature of silver excretion (Furchner, et al. 1968). Radiosilver (^{110}Ag) iodide was removed from the blood two hours after I.V. administration and was slowly excreted through the bile and urine in a nonionic form (Anghileri, 1971). The ratio of urinary-fecal excretion is 0.001 to 0.258 (Furhner, et al. 1968; Kalistratova, et al. 1966; Anghileri, 1969).

Dequidt, et al. (1974) found significant silver excretion in the urine after several I.P. injections of different forms of silver medicinals. Wistar rats given I.P. 12.6 mg/kg silver as the nitrate daily for 5 weeks (apparently a 4-day work week) eliminated 10 to 20 µg/rat/day in the urine. At 5 mg/kg/day silver as silver nitrate for 24 injections within 6 weeks, the urinary silver excretion was 3 to 15 µg/rat/day (average 4 µg). When injections of 29.6 mg/kg colloidal silver were given to rats 11 times within 3 weeks, the urinary excretion was 8 to 24 µg/rat/day (average 12.6 µg). Colloidal silver I.P. injections at 5 mg/kg/day for 24 injections within 6 weeks gave urine containing 2 to 10 µg/rat/day. Silver proteinate I.P. injections (16 within 4 weeks) at 5 mg/kg gave urinary silver contents of 3 to 15 µg/rat/day.

In rats, silver is eliminated from the lungs in 2 or 3 phases. The fastest phase (0.3 to 1.7 days) removes most of the inhaled dose by mucociliary clearance. A second phase and third phase remove absorbed silver, mostly via the liver, with half-lives of about 8 to 15 and 40 to 50 days, respectively.

As of 1964, $^{110\underline{m}}$Ag had been detected 583 times in 186 different individuals in the nuclear industry. Sill, et al. (1964) described the inhalation exposure of 50 peole to activation product $^{110\underline{m}}$Ag when an experimental loop containing silver-soldered thermocouples in the Engineering

Test Reactor was opened. Re-exposure occurred during clean-up procedures, complicating data interpretation; but the calculated effective half-life was about 8 days before recontamination. The source of the $^{110\underline{m}}$Ag and the time of exposure was not the same for all subjects. The individual with the highest body burden of 0.93 uCi had an elimination rate with a half-life of 13 days. Two others had effective half-lives of 17 and 69 days. (The International Commission on Radiological Protection gives 4.9 days for whole-body elimination half-life).

In most cases, maximum activity occurred in the nose, mouth, chest, and lower edge of the rib cage. In almost all the cases, $^{110\underline{m}}$Ag could not be detected in 1,500-ml urine samples, Sill, et al. (1964).

At Harwell, England, a 29 year-old man accidentally inhaled dust from an experimental hole in a nuclear reactor. The burden of radionuclides was below the maximum permissible, but the levels of ^{65}Zn and $^{110\underline{m}}$Ag allowed prolonged study of their retection and distribution (Newton and Holmes, 1966). Whole-body gamma-ray spectrometry on the second day after the accident showed 197 nCi $^{110,\underline{m}}$Ag (and 330 nCi ^{65}Zn). By day 6, 90 percent of the zinc still remained, but only 40 percent of the silver seen on day 2 remained. About 25 percent of the total activity appeared to be confined to the region of the liver. The $^{110\underline{m}}$Ag appeared to be more closely confined to the liver than was the ^{65}Zn on day 16, when individual measurements were made. For 155 days, after which the silver distribution studies were abandoned, the liver was the major site of deposition. The whole-body effective half-life of the 15 percent retained silver was 43 days (biological half-life 52 days).* During the first 100 days, the content in the liver appeared to decrease at about the same rate, but there was a longer-lived component that may have been an artifact from ^{137}Cs. There was no silver in the urine during the first 54 days, but it was present in fecal samples up to about day 300.

The M.S. theses of Phalen (1966) and R.M. Garver (1968) (San Diego State College) reported controlled inhalation studies in which rats were exposed, nose only, to $^{110\underline{m}}$Ag-tagged silver smoke. Clearance from the body was described in two exponential functions of biological half-lives, 8 days and 20 days, indicating two separate body pools of silver (Phalen and Morrow, 1973).

The initial rapid clearance from the lung is on the order of several hours or 1 or 2 days (cited theses above; Skolil, et al. 1961; and Newton and Holmes, 1966). In humans, 80 percent was cleared from the lungs with a biological half-life of 1 day. The half-life for the remainder in the Skolil, et al. (1961) report was 15 days (Phalen and Morrow, 1973).

Phalen and Morrow (1973) studied 6 female beagle dogs who received single acute inhalation exposures to $^{110\underline{m}}$Ag-tagged silver aerosol via tracheal tubes (for 7 to 15 minutes while anesthetized). The method of aerosol generation (by wire explosion) insured well-characterized spherical particles, primarily of metallic silver. The activity median aerodynamic diameters were 0.5 µ. Absolute deposition in the lungs was 1 µg/kg (in text; in the author's abstract the value given is 1 mg/kg).

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* Polachek, et al. (1960), had reported a value of 48 days for liver clearance. The International Commission on Radiological Protection in 1959, however, quoted a value of 15 days.

The solubility rate constants were: in distilled water, 0.1 μg/cm^2/day at 35 to 37°C; and in simulated interstitial fluid, 10 μg/cm^2/day. One could expect 99 percent of the aerosol mass in the lung to dissolve in 2 days.

The activity appeared to clear at about 6 to 8 hours. One dog, exposed for 15 minutes, was sacrificed 6 hours post exposure. There was 96.9 percent of the initial deposit still in the lungs, 2.4 percent in the liver, 0.38 percent in the blood, and 0.02 percent in the stomach. The solubility rate constant in the lung was calculated to be 1 μg/cm^2/day. Perhaps some dissolved silver remained in the lung as a tissue complex.

TABLE 11

Biological Half-Lives (T-1/2) in Days for Clearance in 4 Dogs After Inhalation of Silver Aerosol

	Lung			Liver		Body
Pooled Data	T-1/2	T-1/2	T-1/2	T-1/2	T-1/2	T-1/2 by analysis of excreta (1% in urine)
Dogs 1, 3, 4, and 5	1.7	8.4	40	9.0 (97% of that excreted)	40	8.4 - 12.9

By 3 days, half of the initial amount deposited was gone. Since only 20 percent appeared in the excreta during the first 5 days, most of the silver was not removed by the mucociliary mechanism. Perhaps 90 percent was carried by the blood to the liver. For three dogs, the major silver repositories were the liver, lungs, brain, skin, and muscle. (One of the dogs had larger amounts in bile, liver, and bone.)

Where larger particles are inhaled, elimination may more resemble that observed after oral dosing, when much of the lung deposit has been eventually swallowed.

Camner, et al. (1977) found that inhaled 4-um Teflon particles coated with carbon, silver, or beryllium were cleared from rabbits' lungs (8 to 10 New Zealand rabbits per test) at about the same rate during the first week, despite differences in their toxicity and in the rate of _in vitro_ phagocytosis that had been reported. Presumably, intact particles of the size and lung burden used (aerosol inhaled for only 6 to 8 minutes, resulting in 1 to 10 μCi and 10 to 100 μg deposition) were not actively removed from the lungs by the alveolar macrophages during the first week after inhalation. External measurements of clearance could be made because all of the particles were tagged with ^{51}Cr.

The silver-coating remained 50 percent intact in rabbit serum (replaced daily) at 37°C for 12 days. But in a flow-through system with 10 percent horse serum in saline at 37°C for 8 days, 26 percent of the particles had lost more than half their coatings.

Kent and McCance (1941) followed the excretion of silver for three separate 7-day periods in a woman with severe generalized argyria produced by "washing out her nose for many years with an organic silver preparation." Her negative balances (Table 12) may have been due to desquamation of the silver-containing cells from the alimentary canal lining.

TABLE 12

Silver Balance in a Female With Severe Generalized Argyria

Silver, mg/week	Week 1	Week 2	Week 3
Food	0.05	0	0.7
Feces	1.3	1.5	2.3
Urine	0	0	0
Balance	-1.25	-1.5	-1.6

Enders and Moench (1956) reported that argyric albino rats with varying degrees of heavy silver deposits in the liver and very weak to heavy deposits in the kidney after consumption of a silver medicinal (Targesin) for 3 months, showed progressively less silver in these organs after the silver feeding had been stopped. At 3 months post exposure, the liver deposits in 10 rats were only very weak or entirely absent; and there were no deposits in the kidneys and duodenum. After 6 months on a normal diet, four of the nine rats showed very weak silver deposits in liver, kidney, and/or duodenum.

Buckley and Terhaar (1973) reported that the skin is an excretory organ in generalized argyria with gradual translocation of silver from the general body pool through the dermis and finally into the epidermis as soluble silver. One worker with generalized argyria was studied. Silver appeared to be released from melanin-silver complexes as a soluble ionic form near the surface of the epidermis.

In rats, mice, and rabbits, 99 percent of a one-time oral dose of silver is eliminated within 30 days. Dogs, which absorb 10 percent of the dose, require more than 28 days. Snyder, et al. (1975) for the International Commission on Radiological Protection reviewed the literature pertaining to the silver balance for Reference Man and concluded that his intake in food and fluids is 70 µg/day and his losses include 9 µg/day in urine, 60 µg/day in feces, 0.4 µg/day in sweath, and 0.6 µg/day in hair.

Tipton and Stewart (1970) reported that the range of silver found in the ash of food was 0.5 to 75 mg/kg; of feces, 1 to 115 mg/kg; and urine, 0.0 to 15 mg/kg (analysis by spectrographic procedures).

Kehoe, et al. (1940) found only 0.06 mg/silver/day eliminated in the feces, which was less than the 0.088 mg/day dietary intake of silver. Although silver was detected in the blood of normal Americans, Frenchmen, Mexicans, and Germans, it was not detected in their urine. Almost all silver is excreted in the feces of mammals with only traces in the urine (Gammill, et al. 1950; Scott and Hamilton, 1950). However, silver may be detected in urine in cases of silver poisoning (Sunderman, 1973). Silver has also been detected in nasal and vaginal secretions (Barsegyants, 1967).

Analyses for silver were made on diets and excreta of a husband (Subject B) and wife (Subject A) for 30 days. Subject B had a mean intake of 0.035 mg silver per day and Subject A, 0.04 mg silver per day. Subject A drank five cups of coffee (not analyzed for silver content) per day, had a fecal/urinary silver excretion ratio of 3, and a positive average silver daily balance of 0.007 mg/day (2.6 mg/yr). Subject B drank three glasses of milk per day (analyzed for silver content), had a fecal/urinary excretion ration of 8, and a negative average daily silver balance of 0.054 mg after 30 days (Tipton, et al. 1966)*.

Average human intake from the diet is estimated at up to 0.088 mg/day, (Kehoe, et al. 1940). At that rate, if 100 percent of the silver ingested is retained in the body, 31 years would be required to accumulate 1 g of silver. Based on the data of Tipton and Cook (1963), the average silver content in wet tissue of normal Americans is about 0.05 ppm. The body of a 150-lb human, whose tissue content was 0.05 ppm would contain only 32 mg silver or 3.2 percent of a 21-year ingestion total. It would appear that very little of the silver ingested from nontherapeutic sources is actually retained in the body.

Excretion of radiosilver ($^{110}AgNO_3$) was faster, and a larger percentage of it was excreted in test animals when it was administered orally than when it was injected either I.P. or I.V. More than 90 percent of the carrier-free silver administered by any of these routes was excreted in the feces with at least 90 percent of the orally ingested silver not being absorbed.

In beagle dogs (average age 5.5 years, 12 to 16 kg) given oral doses of 6 μCi ^{110}Ag as the nitrate, about 10 percent of the dose was absorbed. About 70 percent of the absorbed dose had a biological half-life of about 1 month. Dogs retained 1 percent of the dose for at least 4 weeks, (Furchner, et al. 1968).

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* Subject A retained 16 percent of the dietary silver she ingested, but Subject B excreted 2.5 times more silver than he ingested from his diet. (Both A and B excreted about the same amounts of silver in their urine.) Subject B was also in negative balance for copper, barium, and nickel. His medicine intake and occupation were not mentioned nor was the state of his dental restorations.

Female RF mice (8 weeks old, 2 g), given ^{110}Ag as the nitrate I.P., I.V. (tail vein or jugular vein), or orally (12 mice per route) lost half the dose much faster than did the rats of Scott and Hamilton (1950). The rats required 30 days to eliminate 99 percent of the dose, whereas the mice required only 18 days. Almost the entire oral dose (given by stomach tube) was lost by the mice with a biological half-life of 0.125 day. The biological half-life of the remainder was 1.5 days. "The body burden under conditions of chronic oral ingestion would be only about 1/5 of the daily dose," (Furchner, et al. 1966a).

The plots of effective retention versus time of oral doses of ^{110}Ag in 12 mice, 6 rats, 4 monkeys, and 4 dogs showed that within the first day or so, the rate of elimination decreased in the order: rats dogs mice monkeys; but at 5 days, the order was rats mice monkeys dogs; and at 15 to 35 days, the order was mice rats monkeys dogs. The urinary/fecal ratio on day 1 for rats and mice was 0.001; for monkeys, 0.02 (Furchner and Drake, 1968).

When a one-time dose of ^{110m}Ag I (1 µCi ^{110m}Ag in 0.5 g AgI) was force-fed to three cottontail rabbits, 99 percent of the dose was excreted within 3 days, the elimination half-life being 0.48 day. From 8 to 26 percent of the radiosilver entered the cecum (as judged in three rabbits prevented from reingesting their cecal pellets) (Jones and Bailey, 1974).

Four rabbits were fed 0.00042 percent silver in the dry matter of feed as silver iodide complexes prepared to simulate cloud-seeding generator products for 30 days. The concentrations of silver in the dry matter of feces and cecal contents were similar (4.2 to 5.2 mg/kg). The silver content of the dry matter of their livers (0.2 mg/kg) was the same as that in four control rabbits fed a normal diet (0.00001 percent silver), thus absorption was not likely (Jones and Bailey, 1974).

Roy and Bailey (1974) concluded that accumulation of silver in the rumen of any ruminant species upon chronic intake is not likely. The presence of chloride ions, protein, bacteria, and other organic matter in the rumen inhibit the antimicrobial action of silver ions and insure that most of the ingested silver* passes from the rumen in an insoluble form.

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* Silver iodide or silver nitrate at levels simulating 0.0001 percent and 0.01 percent, respectively, in the dry feed were inserted with small amount of feed in nylon bags into fistulas in the rumens of goats.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

The toxicity of silver compounds could be classified as moderate, although large doses of silver compounds may have serious effects (see Table 13). For example, ingestion of 10 g silver nitrate is usually fatal. In humans taking large doses of silver nitrate orally, the patient suffers violent abdominal pain, abdominal rigidity, vomiting, and convulsions and appears to be in severe shock. Patients dying after i.v. administration of Collargol (silver plus silver oxide) showed necrosis and hemorrhages in the bone marrow, liver, and kidney (Hill and Pillsbury, 1939). In the body, silver may be precipitated by protein or chloride ion. Table salt (sodium chloride) is an antidote for silver nitrate poisoning. There is little likelihood of systemic effects in people recovering from toxic doses, but silver may cause degenerative liver changes (Dreisbach, 1963).

The corrosive effect of silver nitrate drops in the eyes of newborn infants to prevent ophthalmia neonatorum has been mentioned above.

The most common noticeable effects of chronic and, less frequently, subacute human exposure to silver or silver compounds are generalized argyria, localized argyria, and argyrosis (argyria of the eye unless stated otherwise). The two most important causes of argyria are medicinal application of silver compounds and occupational exposure. Numerous case histories from Hill and Pillsbury (1939) are summarized in Table 14. Generalized argyria is a slate gray pigmentation of the skin, hair, and internal organs, caused by deposition of silver in the tissues. The degree of pigmentation is highest in areas of the skin most exposed to light,

TABLE 13

Acute Toxic Effects of Silver on Humans (Hill and Pillsbury, 1939)

How Administered	Dosage	Survival Time	Observed Effects	Remarks
i.v. Collargol	36 cc of 12% soln.	3-14 days	Purpura hemorrhagica on the 4th day. Death. Ag chiefly in the reticuloendothelial system.	
i.v. Collargol	32 cc of 5% soln.	3-14 days	Extensive necrosis and hemorrhage of bone marrow, liver, and kidney.	
i.v. Collargol	To fill renal pelvis for X-ray study		Death. Severe hemorrhagic diathesis with parenchymatous hemorrhages in the stomach, intestines, and body cavities.	
i.v. Collargol	10 cc of 2% soln.	5 min	Cyanosis, coma; death due to pulmonary edema.	No Ag found in lungs.
Intravaginally	2 cc unknown concn. of $AgNO_3$		Death.	Abortion attempt. Death possibly not due to $AgNO_3$.
Oral	8 g $AgNO_3$ in soln.		Vomitus contained AgCl.	Patient recovered.
Oral	2-30 g $AgNO_3$	A few hr to a few days	Usually death at dosages 10 g.	10 g is usually fatal, but 30 g has been survived.
Oral metallic Ag	50-260 g		Gastric fullness, anorexia, gastric pain, and/or diarrhea	

but the concentration of silver in the skin from various parts of the body is the same. Silver also accumulates in the blood vessels and connective tissue. Additional manifestations of generalized argyria include: silver coloration of fingernails and conjunctiva and blue halo around the cornea. In localized argyria, only limited areas are pigmented.

Every silver compound in common chemical use has caused generalized argyria. Of 239 recorded cases of generalized therapeutic argyria analyzed by Hill and Pillsbury (1939), 118 were caused by silver nitrate and 28 by Argyrol (mild silver protein), the second most frequent causative agent. Only 19 were caused by i.v. injection of silver arsphenamine. Of 178 cases, in which the route was other than intravenous, 89 were caused by oral intake of silver, chiefly as the nitrate or as colloidal silver plus silver oxide, and another 75 by administration to the nose and throat.

Silver compounds, with the possible exception of silver oxide, are not absorbed through unbroken skin in significant amounts, but absorption occurs through wounds and mucous membranes. Localized argyria of therapeutic origin is relatively rare, usually resulting from topical administration to the conjunctiva, nasal mucosa, tissues of the mouth, or skin ulcers.

Argyrosis involves all eye tissues except the optic nerve. Instillation of 0.25 percent silver nitrate for 3 weeks and instillation of 3 to 5 percent silver colloidal compounds for 5 to 10 weeks have produced argyrosis (Hill and Pillsbury, 1939).

Colloidal silver compounds have been widely used to treat upper respiratory infections, but the amount of silver absorbed and permanently retained by the respirtory tract has not been determined. The total safe period for nasal instillation of colloidal silver compounds is believed to be 3 to 6 months. Colloidal silver compounds in the nose interfere with normal ciliary activity (Hill and Pillsbury, 1939).

Urethral application of Protargol for treatment of gonorrhea resulted in argyria after 2 days, the most sudden onset of argyria reported. Silver nitrate-impregnated compresses applied to abraded skin caused argyria 14 days after the treatment. In only two other cases did argyria result in less than 6 weeks after treatment (Hill and Pillsbury, 1939).

Generalized argyria as an occupational disease was never common. It occurred almost exclusively among silver nitrate makers and is now disappearing due to improved work conditions. Some workers involved in mirror plating, glass bead silvering, silver Christmas cracker manufacturing, photographic plate manufacturing, silver mining, and packaging silver nitrate have developed argyria as a result of ingestion or inhalation of silver fulminate, nitrate, albuminate, and cyanide (Schwartz, et al. 1947). Bronchitis and emphysema have been described in workers with pulmonary argyria, but a cause-and-effect relationship has not been established (Gafafer, 1964).

Argyrosis occurred in all cases of argyria caused by occupational exposure and was generally more pronounced than therapeutically produced argyrosis. Localized argyria is rare, usually resulting when silver compounds contact broken skin or mucous membranes (Hill and Pillsbury, 1939). It has occurred in workers who handle metallic silver in filing, drilling, polishing, turning, engraving, forging, soldering, or smelting operations. Local argyrosis has occurred in electroplaters, firecracker makers, silver mirror manufacturers, etc. Silver polishers exposed over long periods, sometimes exhibit increased densities in their lung X-rays due to silver impregnation of the elastic membranes of the pulmonary vessels. Pigmentation occurs slowly in workers who develop localized argyria--50 percent of the workers have been employed 25 years or more. The time of the onset of pigmentation has varied 2 to 38 years (American Conference of Governmental Industrial Hygienists, 1971; Hill and Pillsbury, 1939).

In three cases, post-mortem examination showed the distribution of silver in the tissues of persons having argyria resulting from occupational exposure was the same as the distribution of silver in tissues of those having therapeutic argyria (Hill and Pillsbury, 1939).

Table 14 includes cases of argyria from occupational as well as iatrogenic exposure.

TABLE 14

Argyria

Observed Effect	Ag Compound	Exposure Conditions	Length of Exposure	Time Until Appearance of Argyria	Ag Intake or Total Dose	Ag Excretion	Remarks	Reference
Increased densitries in lung X-rays	Ag particles	Silver polishers	Long periods				Ag impregnation of vascular elastic membranes	Am. Conf. Gov. Indus. Hygienists (1971)
Localized argyria	Ag particles	Penetration of fine particles						Am. Conf. Gov. Indus. Hygienists (1971)
Generalized argyria	Ag salts	Ingestion or inhalation of Ag salts						Am. Conf. Gov. Indus. Hygienists (1971)
Argyrosis		1-2 mg Ag/m^3 in air during spraying operations in manufacturing Ag varnish and in silvering radio-tech. parts					11 were affected in upper respiratory passages. 9 in conjunctiva or cornea.	Am. Conf. Gov. Indus. Hygienists (1971)
Generalized argyria, possibility of	Ag in air	Breathe 10 m^3 air/day; retention of 50% of Ag (assumed)	20 years		5-fold the recommended TLV, 0.05 mg/m^3, would lead to accumulation of 1.2 g Ag.			Am. Conf. Gov. Indus. Hygienists (1971)
Generalized argyria		Medication or industrial exposure			Lung and G.I. tract	Primarily in feces; only traces in urine.	Absorbed via G.I. tract or by dust inhalation.	Browning (1961)
Generalized argyria						Very slight, over 3 week-long periods.		Browning (1961)
Argyria - no recognizable health disturbances							Possible cause of kidney lesions with consequent dangers of arteriosclerosis and lung damage but not fibrosis.	Browning (1961)
Pulmonary argyria							Often have bronchitis and emphysema, but no cause-effect relationship has been established.	Gafafer (1964)

TABLE 14 (Continued)

Observed Effect	Ag Compound	Exposure Conditions	Length of Exposure	Time Until Appearance of Argyria	Ag Intake or Total Dose	Ag Excretion	Remarks	Reference
Lung pigmentation	Ag and Fe_2O_3	Worked as a silver finisher.					Due primarily to Fe, but Ag present.	Johnstone and Miller (1960)
Generalized argyria	$AgNO_3$	Administered orally to treat epilepsy and G.I. symptoms.	Weeks to 20 years	E.g., 2 years after taking 600 g for 1.2 year	9- 1,000 g			Hill and Pillsbury (1939)
Generalized argyria	Protargol	300-g soln. instilled into urethra daily	2 days	3 days				Hill and Pillsbury (1939)
Generalized argyria	$AgNO_3$, stick	Local application for sore throat and tongue ulcers	0.5-20 years	E.g., 1 year (when used for 3 years)				Hill and Pillsbury (1939)
Generalized argyria	Collargol	Administered orally to treat pulmonary tuberculosis	E.G., 5 years (260 g Ag)	1 year	50-530 g			Hill and Pillsbury (1939)
Generalized argyria	Ag arsphenamine	i.v.	2-10 years	16 months to 9 years	0.91-7.6 g			Hill and Pillsbury (1939)
Generalized argyria							201 cases from 1700 to 1939	Hill and Pillsbury (1939)
Localized argyria							17 cases from 1700 to 1939	Hill and Pillsbury (1939)
Argyrosis							57 cases from 1700 to 1939	Hill and Pillsbury (1939)
Industrial argyrosis							12 cases from 1700 to 1939	Hill and Pillsbury (1939)
Localized argyria of gums	Dental alloy	During preparation for a dental crown					Burton (1970)	
Mottled pigmentation		AgC:CH	Explosion				Caused blue pigmentation	Orentreich and Pearlstein (1969)

Several toxic effects, only indirectly attributable to silver, have been reported from use of silver compounds in treatment of burn patients. Most of them occur within a few days of initial treatment and are readily corrected by appropriate treatment; the duration of silver treatments probably seldom extends into the chronic range ($\geq$ 13 weeks).

Because of the hypotonicity of the 0.5 percent silver nitrate dressings and the tendency to precipitate as silver chloride, electrolyte imbalance may occur in a few hours (Wood, 1965). Electrolytic disturbances are also occasionally found in patients treated with silver sulfadiazine (Burke, 1973). For that reason, the electrolytes in the patient's blood are closely monitored and supplemented when necessary. Severe electrolyte depletion is especially common in children during prolonged use of 0.5 percent silver nitrate in burn therapy (Bondoc, et al. 1966).

Methemoglobinemia is sometimes induced in patients treated with silver nitrate because of the reduction of the nitrate to nitrite by bacteria in the patient's skin, not because of the presence of nitrite in the original solution. Cultures of endobacteria from a burn patient exhibiting methemoglobinemia readily reduced nitrites (Strauch, et al. 1969a). An absorptive surface such as a granulating wound or damaged skin is also needed (Strauch, et al. 1969b). Strauch, et al. (1969a) recommended that discontinuation of silver nitrate therapy in patients with up to 30 percent methemoglobinemia would return patients' hemoglobin levels to normal within 24 to 72 hours. However, if the level is greater than 30 percent the patient must be actively treated with methylene blue.

Silver sulfadiazine (Silvadene, Marion Laboratories, Kansas City, Missouri) is used increasingly to prevent infections from Pseudomonas aeruginosa and other bacteria in treatment of burn patients. It is preferred to silver nitrate treatments because it does not deplete the body of sodium, chloride, or potassium.

Henderson (1975) stated that the finding of leukopenia in burn patients being treated with silver sulfadiazine (Silvadene cream) was not due to the treatment, but to the thermal injury itself. Daniels, et al. (1975, cited by Henderson) had found that depressed white blood cell count and suppressed immune response were often seen in burn patients. Gayle and Haynes (1976, cited by Kiker, et al. 1977) had seen marked leukopenia in burn patients treated with silver sulfadiazine. Kiker, et al. (1977) performed a double-blind study with a nonantimicrobial placebo in the control group to determine if the leukopenia was due to the silver sulfadiazine therapy or to the thermal injury. Thus, 60 juvenile patients with a mean area burned of 48 percent of the body surface and treated with the placebo showed a white blood cell count of $11.8 \pm 2.5 \times 10^3/mm^3$. The 69 juvenile patients (52 percent mean area burn) receiving silver sulfadiazine treatment had a white blood cell count of $12.2 \pm 2.1 \times 10^3/mm^3$. There was no significant difference in the white blood cell count of the two groups ($p > 0.05$); six placebo-treated patients and five silver sulfadiazine-treated patients developed leukopenia (WBC $< 5,000/mm^3$). In a second similar study with 175 patients receiving silver sulfadiazine, 5.7 percent developed leukopenia. In all cases, the leukopenia resolved itself without discontinuing the therapy.

Valente and Axelrod (1978) maintain that the leukopenia observed during silver sulfadiazine therapy is due to the sulfadiazine portion of the drug (most of the silver remains at the wound bound to tissue and bacterial proteins and DNA), not the injury. They aspirated the bone marrow of a burn patient exhibiting leukopenia on two occasions within 48 hours of treatment with Silvadene and noted cell maturation arrest.

Renal injury, sometimes fatal, and sensitivity following sulfonamide therapy is well-known. Owens, et al. (1974) reported the first case of nephrotic syndrome apparently due to topical application of silver sulfadiazine. The electron-dense deposits seen in the glomerular basement membrane suggested an immune-complex mechanism. No attempt was made to identify the deposits as silver since precipitation of crystals has been observed during other sulfonamide-induced renal damage.

Fox (1973), when asked to discuss side effects that had occurred in the 5 years of use of silver sulfadiazine cream in burn treatment, remarked that two cases of apparent skin sensitivity had come to his attention.

Aside from burn therapy and use of medications applied to mucous membranes, silver metal has been used in surgery. A tumor around a surgical silver clip is discussed below. Silver points have been used for years to induce apical bone healing in dental surgery. Because of the recognized cytotoxicity of silver corrosion products, Weissman (1975) recommended that titanium points be substituted for silver.

Argyrosis of the cornea in workers who handle silver nitrate may be accompanied by turbidity of the anterior lens capsule and a disturbance of dark adaptation. Deposition of silver in the eye does not usually result in loss of vision (Browning, 1961).

Two silver nitrate workers afflicted with argyrosis of the lung showed mild chronic bronchitis with silver impregnation in the walls of the middle and upper region of the nasal mucosa. In a more severe case, the bronchial mucous membrane also showed basal membrane deposits and some squamous metaplasia. There was less evidence of phagocytosis than in the nasal mucosa and no hazard of fibrosis. Pigmentation was comparable with that of anthracosis and siderosis (Browning, 1961).

Grant, et al. (1975) analyzed by atomic absorption spectrophotometry the lung tissues of 11 mummified subjects from northern Peru, believed to have been involved in hard-rock silver mining and/or ore refining* in the period 1500 to 1600 A.D. High levels of mercury were found in most tissues, but there was not any statistical correlation between the concentrations of mercury or lead and lung disease. A moderate correlation between lung disease and silver was found.

Marks (1966) reported the case of a 33 year-old woman, a radiographer for 10 years, who exhibited a contact dermatitis under her contaminated watch strap. Patch tests showed sensitivity to the thiosulfate complex of silver iodide, fixing fluid which had contacted silver (but not unused fixing fluid), and 1 percent silver nitrate. The sensitivity was assumed, therefore, to be due to ionic silver.

* Lead was used in the refining process prior to 1571, whereas mostly mercury was used thereafter.

Marks had found only one case in the literature of contact dermatitis due to silver. Gaul and Underwood (1948, cited by Marks) reported a dermatitis in a 27-year-old man who had sensitized himself by using a silver nitrate solution on his feet. In sensitivity tests, he reacted to old 10 percent silver nitrate solution (but curiously not to fresh solution), silver foil, and silver proteinate. Since lists of allergens for patch tests sometimes included 5 or 10 percent silver nitrate solutions, Marks suggested that allergic contact dermatitis was more prevalent when silver nitrate topical treatments were more common.

Zech, et al. (1973) attributed a nephrotic syndrome in an obese, argyric 73-year-old man to silver deposits in the kidney. The man had used a silver-containing mouthwash or gargle for 10 years (1955 to 1965), presumably corresponding to the absorption of a total amount of 88 g of silver. The patient showed respiratory insufficiency and a nephrotic syndrome with proteinuria, elevated a_2 macroglobulins, and glomerular (but not tubular) involvement. Silver deposits were found in the glomerular basement membrane.

The toxicity of silver to species other than mammals or birds will not be discussed because of its inapplicability to human toxic effects.

Acute effects from silver in mammals are usually associated with I.V. administration. For example, silver nitrate has been used frequently since 1932 to produce acute pulmonary edema for study. Dogs injected with 0.5 ml of 10 percent $AgNO_3$/kg ($\sim$ 32 mg Ag/kg) into the left ventricular wall or the pulmonary artery developed the edema, myocardial ischemia and lesion, hypertension, and swelling and necrosis of wall and endocardium. Genesis of pulmonary hypertension and edema by silver nitrate depends on its entering the pulmonary circuit, and the mechanism involved is probably stimulation of vagal terminations (Sales and Silva Duarte, 1962). Intravenous injections of silver nitrate in dogs produced hemodynamic disturbances resulting in pulmonary edema, with circulatory hypoxia causing death (Mazhbich, 1961).

Hill and Pillsbury (1939) reviewed the early literature on the toxic effects seen in animals given various medicinal forms of silver. When inorganic compounds were given i.v., the effects were chiefly on the central nervous system. The animals receiving lethal doses showed weakness, rigidity, and contractures in the legs, loss of voluntary movements, and interference with cardiac blood supply. LD_{50} data apparently were not calculated.

The oral LD_{50} for silver sulfadiazine in CF-1 mice has not been determined, but the LD_{90-100} was $> 1,050$ mg (Wysor, 1975b and 1977).

The I.P. LD_{50} (30 days) for Ag^+ as the nitrate in male Swiss albino mice (21 ± 2 g) is 13.9 mg/kg, indicating that Ag^+ is 345 times more toxic than Na^+ (as the chloride) (Bievenu, 1963).

Rabbits receiving 20 injections on their depilated backs of a silver salt dissolved in distilled water (0.01 M) showed papules which had a minimum diameter of 5 mm within 24 hours. Of the group I metals tested, only silver and gold produced skin reactions (gold at 0.1 M concentration) (Muroma, 1961).

Some of the toxic effects of Ag^+ and other heavy metal ions may be due to their alteration of cyclic adenosine monophosphate (AMP) metabolism, which would be expected based on in vitro experiments by Nathanson and Bloom (1976): an 8 μM solution of silver nitrate caused 50 percent inhibition of adenylate cyclase in a rat cerebellar homogenate, and a 30 μM solution caused 58 percent inhibition of phosphodiesterase, in a 0.1 uM solution of cyclic AMP.

Several acute toxicity studies in animals are summarized in Table 15.

Most of the subacute dosing experiments with silver compounds are summarized in Table 15. Except for the corrosive nature of low doses of silver nitrate, most of the other compounds tested were reasonably tolerated by the animals in periods up to 71 days.

Yoshikawa (1970) reported that mice given pretreatments with certain heavy metals, including silver, lead, cadmium, and mercury, developed a tolerance to a lethal dose* of the metal as shown by fewer deaths in the pretreated mice compared with mice that were not pretreated. Thus, when 10 male ICR mice were given an i.p. dose of 3.5 mg Ag/kg as silver nitrate before the challenge dose of 35 mg/kg 24 hours later, only three of the pretreated mice died within 7 days, compared with eight of the nonpretreated mice.

Dymond, et al. (1970) implanted wires of several metals and alloys including pure silver into the brains of cats for 2 months. Silver produced a toxic effect as shown by a very large scar with a large component of glial elements. The author cited other reports wherein silver or silver/silve chloride was toxic as a brain implant. (Other studies wherein implants were maintained for longer than 2 months are described below under chronic studies).

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* The pretreatment dose was 10 percent of the challenge dose. The challenge dose was "about 70 to 80 percent lethal doses," presumably the LD_{70-80}.

Olcott (1950) gave rats either silver nitrate or thiosulfate in 1:1,000 concentration (635 mg Ag/liter if $AgNO_3$ and 660 mg Ag/liter if $Ag_2S_2O_3$) in their drinking water for up to 30 months. The finding of hypertrophy of the left ventricle in a statistically significant number of rats was presumed to indicate that the rats had developed vascular hypertension, possibly due to thickening of the basement membranes of the renal glomeruli.

Olcott (1948) had given rats 1:1,000 concentration of silver nitrate or thiosulfate in their drinking water for their lifetime, beginning shortly after weaning, without observing any shortening of the lifespan. Skin pigmentation was not observed, but the internal organs (the pancreas was especially dark) and the eyes were darkened by silver deposits. Absorption was apparently via the small intestine based on the large amount of silver found in its villi. The deposition of silver in internal organs and tissues usually resembled that seen in humans with argyria.

TABLE 15

Acute Effects of Silver on Terrestrial Animals

Organism	How Administered	Dosage	Survival Time	Percent of Sample	Observed Effects	Remarks	References
Rats	s.c. injection $AgNO_3$	7 mg/kg body wt.			Affected testis histology and spermatogenesis. Peripheral tubules affected and some central tubules completely degenerated after 18 hr. Some tubules recover. Duct system seldom fully recovers.	Marked deformation of tubules at head of epididymis. Epithelial cells appeared swollen. Spermatogenesis active.	Hoey (1966)
Rats	s.c.	0.35 or 0.7 mg/ 100 g body wt.			Decreased threshold of electrical stimulation of epileptiform convulsions.	No clinical symptoms of intoxication.	Fedotov (1969)
Rabbits	i.v. Cryptargol	1-3 cc soln. contg. 0.1 g Ag/cc	4-48 hr.		Congestion of kidneys, tubular swelling, and/or glomerular necrosis.		Hill and Pillsbury (1939)
Rabbits	i.p. $AgNO_3$	20 mg/kg in neutral soln.	2 hr		Death in coma. Degenerative aspects and Ag granules in liver parcenchyma and kidney tubules.	No abnormalities in heart, lungs, brain or adrenals.	LaTorraca (1962)
Guinea pig	2 ml i.p. $AgNO_3$	0.239 $\underline{M}$ $AgNO_3$	1-7 days		Death.		Wahlberg (1965)
Dogs	i.v. Collargol	200-300 mg			Well tolerated.		Shouse and Whipple (1931)
Dogs	i.v. Collargolum (1% emulsion of Ag)	500 mg	12 hr		Pulmonary edema, anorexia, profound anemia, active hyperplastic bone marrow.	Also had weight loss and weakness.	Browning (1961)
Dogs	i.v. Collargol	500 mg	24 hr.		Death, hemolysis, lung edema	A dog given 2,600 mg Collargol over 4 months in doses of 20-600 mg died after the last injection of 600 mg.	Shouse and Whipple (1931)
Dogs	i.v. Ag albuminate	0.03 g	0.5 hr.		Death.		Hill and Pillsbury (1939)

TABLE 15 (Continued)

Organism	How Administered	Dosage	Survival Time	Percent of Sample	Observed Effects	Remarks	References
Dogs	i.v. $Ag_2S_2O_3$	0.2 g in 60 cc H_2P			Death in convulsive seizures, pulmonary edema.	At lower dosages: anesthesia and paralysis of hind legs followed by increased bronchial secretion and asphyxial death.	Hill and Pillsbury
Dogs	i.v. $AgNO_3$				Death due to mechanical asphyxia.		Hill and Pillsbury (1939)
Dogs	i.v. $AgNO_3$	32 mg			Death.		Hill and Pillsbury (1939)
Dogs	i.v. Argyrol	3 mg/kg	$\leq$ 18 hr		Death despite regular respiration while in coma.		Hill and Pillsbury (1939)
Dogs	i.v. Argyrol	4-5 mg/kg			Also had edema of lungs and intestinal hemorrhages.		Hill and Pillsbury (1939)
Dogs	i.v. Colloidal Ag	100 mg			Hemolysis.		Hill and Pillsbury (1939)
Dogs	$AgNO_3$ placed directly in stomach	2.3-2.6 g	A few days if vomiting is impeded.		Death if vomiting prevented.		Hill and Pillsbury (1939)
Horses	i.v. (?)	$AgNO_3$			Death, hemorrhage and thrombi of heart and kidneys.		Hill and Pillsbury

TABLE 15 (Continued)

Organism	How Administered	Dosage	Survival Time	Percent of Sample	Observed Effects	Remarks	References
Rabbits	i.v. Cryptargol daily	0.6 cc soln. contg. 0.1 g Ag/cc			No albumin or casts in urine.	Administered for 71 days.	Hill and Pillsbury (1939)
Rabbits	i.v. Ag arsphenamine (14.5% Ag)	66.7 mg/kg for 47-70 days			More Ag retained by animals losing weight. Most showed a gradual increase in hemoglobin and red blood cells. No toxic effects or discoloration.	Minimum dosage 277 mg in 47 days. Maximum dosage 2,363 mg in 70 days.	Hill and Pillsbury (1939)
Dogs	i.v. Collargol	1,300-1,500 mg over 3-7 days			Tolerated.		Shouse and Whipple (1931)
CF-1 Mice	Oral or s.c. silver sulfadiazine	1,050 mg/kg/day for 30 days			Cured mice of their infection by Plasmodium berghei within 5 days even after a splenectomy. Also effective against systemic infection by Pseudomonas aeruginosa. The mice did not show any histological pathology, weight loss, or abnormal behavior. There was a local granulomatous lesion at the s.c. injection site.		Wysor (1977) Wysor (1975b)
Rats	s.c. Ag-contg. substance not identified	3,5-7 mg/kg for 14 days			Decreased threshold of epileptogenic effect of electrical stimulation.		Fedotow (1968)

The following chronic studies are arranged in order of the lowest chronic dose administered.

Albino rats receiving doses of 0.00025 and 0.0025 mg electrolytic silver per kilogram body weight in their drinking water for 11 months did not show any changes in conditioned-reflex activity. The dose 0.0025 mg/kg corresponds to 0.05 mg/liter in the water (Barkov and El'piner, 1968). Doses of 0.025 (0.5 mg/l) and 0.25 mg Ag^+/kg in rats did affect the conditioned reflex activity. These doses during 11 months also lowered the immunological activity of rabbits as judged by increasing phagocytosis by blood leukocytes. Pathological changes were noted in vascular, nerve, brain, and spinal cord tissues (Barkov and El'piner, 1968).

None of the doses induced changes in the hemoglobin content, number of erythrocytes, the leukocyte formula, the protein-forming function of the liver, and the content of thiol groups in the blood (Barkov and El'piner, 1968).

Rats receiving 0.05 mg Ag^+/liter in their drinking water for 5 months showed no effect on gastric secretion; blood serum enzymes; or morphology of the stomach, intestine, liver, and kidney. Pathomorphological changes in stomach, small intestine, and liver were noted, however, in rats receiving 20 mg Ag^+/liter. Blood serum asparagine transaminase and alanine transaminase were increased $>$ 2 and 2.4 times over the level in the control group, respectively, and growth was depressed 36 percent at the higher concentration (Maslenko, 1976).

Pak and Petina (1973) gave 94 white rats of both sexes 0.1, 20, and 50 mg Ag^+/liter for 4 and/or 6 months while the 20 controls drank the Moscow water supply. When Ag^+

was supplied as silver nitrate, after 4 months there was a small decrease in the -SH groups in the blood serum (51.2 versus 57.0 $\mu\underline{M}$ in the controls) at 50 mg/liter. Anodically produced silver of the same concentration did not produce this effect. But after 6 months, both forms of Ag^+ at 20 mg/liter depleted the -SH groups: ionic silver, 31.2 $\mu\underline{M}$; $AgNO_3$, 35.3 $\mu\underline{M}$; and controls, 50.0 $\mu\underline{M}$. At 4 months, the 0.1 mg/liter concentration had actually increased the concentration of -SH groups in blood serum to 63.0 to 64.0 $\mu\underline{M}$.

Kul'skii, et al. (1973) reported that 0.100 to 0.200 mg Ag^+/liter in the drinking water of test animals did not affect the antimicrobial and antiviral immunity formation in the animals (see Savluk, 1973, below). There was also no effect on the ratio of the blood-forming elements (see Savluk and Moroz, 1973, below), the protein content, the functional state of the spleen, or conditioned-reflex development (see Khorchenko and Stepanenko, 1972, and Zapadnyuk, et al. 1973, below).

The function of the reticuloendothelial system in the manufacture of specific protective factors in rats receiving 0.2 and 20 mg Ag^+/liter in their drinking water for 8 months was not altered, but albino mice receiving the higher dose showed reduced absorptive capacity of the reticuloendothelial system (Savluk, 1973).

Kharchenko and Stepanenko (1972) (see als. Kul'skii, et al. 1972) found no change in conditioned-reflex activity in male (8 or 15 or 16 per group) albino rats given drinking water with 0.2 to 0.5 mg Ag^+/liter for 6 months and insignificant changes in rats given 2 mg Ag^+/liter. However, at 5 to 20 mg/liter, intoxication was observed beginning the

25th to 27th day. At that time, there were no conditioned reflex changes. A dose of 20 mg/liter had inhibited the intensity and prolonged the latent period of the cortical response to stimuli by the end of the second month. The latent period of the conditioned reflex was 2.5 times that of the controls. On prolonged ingestion, there occurred an increase of excitability, an increase in the number of intersignal reactions, differentiation disinhibition, and disturbances in mobility and equilibration of main nervous processes. After 5 to 6 months at 20 mg/liter, the inhibition of the positive conditioned reflexes again occurred, with increasing intensity.

Male albino rats (five), drinking water containing 20 mg Ag^+/liter for 8 months, showed a significant decrease in the rate of their escaping from an aqueous labyrinth from the rate of the controls. The repressing effect on the rate was less at 2 mg/liter and even less at 0.5 mg/liter, but those rats receiving 0.2 mg Ag^+/liter (0.01 mg Ag/kg body weight) showed no difference (Zapadnyuk, et al. 1973).

Savluk and Moroz (1973) studied changes in the blood of albino rats (240 total) receiving electrolytically produced silver ions for 3 months in their drinking water at 0.2 mg Ag^+/liter (0.03 mg/kg/day) and 20 mg Ag^+/liter (3.0 mg/kg). No changes were noted in the hemoglobin; number, color, and form of the erythrocytes; the color index of the blood; and the precipitation reaction of the erythrocytes. The increase in the number of leukocytes in the test rats was statistically insignificant. Upon electrophoretic analysis, there was no significant difference in the protein fraction ratio of the blood of the rats receiving 0.2 mg/liter from that of the controls. There seemed to be an increase in gamma and betaglobulin fractions. At 20 mg Ag^+/liter, there still was no statistically significant difference in the ratio of protein fractions in comparison with that of the controls; yet the slight increase in the globulin fractions was accompanied by a lowering of the amount of albumins and total protein in the blood.

A slight change in protein metabolism shown by changes in the amount of proteins in each fraction in the serum reverted to normal by 2 months after the end of silver intake.

The 0.2 mg/liter animals showed no change in liver function, but the higher concentration lowered the weight of both the liver and whole animal. It was concluded neither level was toxic to the liver.

The higher concentration increased the amounts of almost all 16 free amino acids determined in the blood serum (Savluk and Moroz, 1973).

The changes in brain nucleic acids of rats after chronic intake of silver as determined by Kharchenko, et al. (1973b) are shown in Table 16. Male albino rats (three), drinking water containing 0.5 mg Ag^+/liter for 6 months from the time they were 3 months old, showed increased body weight compared with the controls, lowered nucleic acid content in the brain, and increased weight of brain per cell nucleus (thus, hypertrophy of the cells). After 12 months on this regime, both brain and body weights of three rats were significantly higher than those of the controls, the content of brain nucleic acids was higher, the weight of brain per nucleus was about the same as those of the controls, and the RNA/DNA ratio was higher. These effects were generally more pronounced, but in the same direction in rats (three) receiving 2 mg Ag^+/liter for 12 months. However, the weight

TABLE 16

Quantitative Changes in Nucleic Acids in the Brain of Rats After Intoxication with Silver for 6 Months

Concentration of Silver, mg/l	Weight of Animal, g	Weight of Brain, g	Concentration of Nucleic Acids in Brain, mg %		Contents of Nucleic Acids in Brain, mg		Number of Nuclei in Brain, 10^6	Weight of Brain/ Nucleus	Content of DNA/ 100 mg Dry Weight of Brain	Ratio of the RNA/DNA Content in Brain
			DNA	RNA	DNA	RNA				
Control	249 ± 20	1.93 ± 0.07	13.9 ± 1.6	12.7 ± 0.8	2.75 ± 0.36	2.57 ± 0.2	444 ± 59	4.8 ± 0.8	0.141 ± 0.016	1.0 ± 0.19
0.5	274 ± 23	1.92 ± 0.05	12.0 ± 0.7	8.5 ± 1.8	2.33 ± 0.03	1.73 ± 0.38	376 ± 13	5.1 ± 0.3	0.119 ± 0.021	0.75 ± 0.18
P	0.556	0.091	0.683	0.920	0.695	0.90	0.695	0.39	0.561	0.478
20	278 ± 57	1.95 ± 0.14	19.3 ± 0.5	16.2 ± 1.1	3.79 ± 0.26	3.32 ± 0.29	612 ± 30	3.2 ± 0.1	0.194 ± 0.007	0.88 ± 0.08
P	0.423	0.099	0.95	0.95	0.941	0.922	0.95	0.906	0.95	0.512

AFTER INTOXICATION WITH SILVER FOR 12 MONTHS

Concentration of Silver, mg/l	Weight of Animal, g	Weight of Brain, g	Concentration of Nucleic Acids in Brain, mg %		Contents of Nucleic Acids in Brain, mg		Number of Nuclei in Brain, 10^6	Weight of Brain/ Nucleus	Content of DNA/ 100 mg Dry Weight of Brain	Ratio of the RNA/DNA Content in Brain
			DNA	RNA	DNA	RNA				
Control	313 ± 42	1.9 ± 0.12	15.7 ± 0.9	16.9 ± 2	3 ± 0.2	3.4 ± 0.3	487 ± 31	3.9 ± 0.13	0.159 ± 0.009	1.12 ± 0.08
0.5	379 ± 28	2.1 ± 0.1	15.5 ± 0.8	17.7 ± 1.2	3.3 ± 0.1	4 ± 0.1	589 ± 13	4 ± 0.2	0.156 ± 0.008	1.19 ± 0.02
P	0.720	0.806	0.124	0.264	0.785	0.849	0.785	0.073	0.181	0.529
2	326 ± 44	2.1 ± 0.08	18.2 ± 0.49	18.8 ± 1.9	3.9 ± 0.1	4.1 ± 0.5	625 ± 13	3.4 ± 0.1	0.184 ± 0.006	1 ± 0.1
P	0.216	0.766	0.892	0.466	0.95	0.720	0.95	0.893	0.897	0.264
20	338 ± 84	1.9 ± 0.1	12 ± 1.2	8 ± 1.2	2.3 ± 0.3	1.6 ± 0.1	374 ± 47	5.2 ± 0.6	0.121 ± 0.011	0.7 ± 0.1
P	0.195	0.444	0.921	0.95	0.859	0.99	0.862	0.859	0.924	0.95

of brain per nucleus and the RNA/DNA ratio was lowered (that is, DNA content had increased more than the increase in RNA) (Kharchenko, et al. 1973a and 1973b).

After 20 mg Ag^+/liter for 6 months, all of the indices were increased except that the weight of the brain per nucleus and the RNA/DNA ratio was reduced. After 12 months on this concentration, all indices were reduced compared with those of the controls except for increased body weight, identical brain weight (which would indicate dystrophy since brain weight was higher at 6 months), and increased weight of brain per nucleus (Kharchenko, et al. 1973b).

Apparently, as the animals aged and silver accumulated, the presumed protective action of increased content of brain nucleic acids was weakened. An increase in the number of nuclei in the brain apparently was also a protective action. Lowering the RNA/DNA ratio reflected the lowering of metabolic reactions in the brain tissues. In the controls, the intensity of nucleic acid metabolism in the intact animal was somewhat increased with growth (Kharchenko, et al. 1973b). The authors' interpretation of these results is open to question. An increase in brain DNA may well indicate tissue damage.

Klein (1978) stated that Just and Szniolis (1936) had observed immunological changes in test animals and had concluded that silver might be harmful to humans in this regard. There is no indication in the paper cited of immunological changes. For an unstated time, rats ingested up to 1 mg Ag/liter in their drinking water. At concentrations below 0.4 mg/liter, the rats appeared in good health, and dissection did not reveal any apparent pathological changes. At 0.4 mg/liter, small hemorrhages were detected in the kidney; and there was blood pigment accumulated in some glomeruli, larger vessels, and walls of the caniculi in which hemorrhages had occurred. At 0.7 mg/liter, there were large amounts of blood pigment in fresh and old tissue extravasations; and the changes in the kidney were more marked. At 1 mg/liter, pigment was finally observed in the spleen and the changes in the liver and kidney were more pronounced.

At a much higher level of silver--60 mg/kg as silver nitrate or Targesin (equivalent to 1,200 mg/liter if given in drinking water to rats) for "several months", silver nitrate-fed animals showed degenerative kidney changes; the Targesin-fed rats did not (Enders and Moench, 1956).

Bates, et al. (1948) cited by Chusid and Kopeloff (1962) had found that silver implants in the brain resulted in formation of a surrounding fibrous capsule, necrosis, and infiltration of the cortex and meninges. Fischer, et al. (1957, cited by Chusid and Kopeloff, 1962) had warned that silver or copper wires were unsuitable for use in human depth electroencephalography since they had observed damage and necrosis around such wires in cats' brains. Chusid and Kopeloff (1962) inserted a spheroid pellet (3-5 mm diameter) of silver into the brain of one monkey, which survived 21 months. The monkey showed spike and slow changes in the electroencephalogram and exhibited a brain lesion classified as a meningocerebral cicatrix in contrast to a necrotizing foreign body reaction, produced by such elements as antimony, cadmium, copper, mercury, and nickel.

To summarize chronic drinking water experiments: rats given 0.05 mg/liter silver in their drinking water for 11 months showed no changes in conditioned-reflex activity and for 5 months, no effect on gastric secretion, blood serum enzymes, liver, or kidney. A concentration of 0.1 mg/liter or 0.2 mg/liter also appeared to have no effects; but at ≥ 0.4 mg/liter, hemorrhages were observed in the kidneys. At 0.5 mg/liter for 11 months, conditioned reflex activity and immunological resistance were lowered, and brain nucleic acid content was increased. A concentration of 2 mg/liter caused similar effects. By 20 mg/liter, numerous physiological changes, including growth depression, were evident. Thus, concentrations of silver ions in drinking water up to 0.2 mg/liter (the maximum allowed by Swiss authorities for 38 years) caused no deleterious effects within time periods up to 11 months. Ill effects appeared at 0.4 mg/liter, and by 0.5 mg/liter, conditioned-reflex activity and immunological activity were reduced.

Synergism and/or Antagonism

Silver exhibits antagonism to selenium, vitamin E, and copper, inducing deficiency symptoms in animals fed adequate diets or aggravating deficiency symptoms when the animals' diet lacks one or more of the nutrients. The effects have been described in dogs, sheep, pigs, rats, chicks, turkey poults, and ducklings.

Shaver and Mason (1951) first noted the toxicity of silver to vitamin E-deficient rats. On 1,500 mg/liter silver as the nitrate in their drinking water, the animals developed muscular dystrophy, liver necrosis, and increased mortality. All 23 rats on the low-E diet died within 18 to 40 days except for one survivor for 7 months. Diplock, et al. (1967) and Grasso, et al. (1969) found the liver necrosis in rats induced by silver was indistinguishable from that arising in animals that were deficient in vitamin E and/or selenium. Grasso, et al. (1969) also noted necrosis in the brain followed by necrosis of the nuclei, endoplasmic reticulum, and mitochondria. Bunyan, et al. (1968) reported that 3 mg/kg cyanocobalamin in the diet prevented liver necrosis at 0.0130 percent silver in the drinking water or diet.

A silver-induced increase in the selenium content of the mitochondrial fractions of the liver of vitamin E-deficient rats was noted by Diplock, et al. (1971). Grasso, et al. (1969) had observed proliferation of lysosomes in the livers of silver-treated rats deficient in vitamin E. Diplock, et al. (1971) speculated that Ag_2Se accumulation in the lysosomes of the liver mitochondrial may explain the increased selenium retention in the mitochondrial fraction in silver-treated rats, although the total amount of selenium in the liver was lowered. They further speculated that perhaps an insoluble silver salt of selenium is formed in the intestine to reduce its absorbability and, therefore, reduce its absolute amount in the liver. Silver-treated rats exhibited greater fecal excretion of ^{75}Se from the diet.

Rats fed diets containing 0.00005 percent selenium and 76 or 751 mg/liter silver in their drinking water for 52 days showed liver glutathione peroxidase levels 30 percent and 4 percent respectively, of the concentration in control rats given the vitamin E-deficient diet with 0.00005 percent selenium as sodium selenite but no silver.* Howeverever, the selenium dietary supplement did improve the growth and survival of rats given 751 mg/liter silver (but increased the silver content of liver and kidney) and entirely prevented the growth depression seen in rats given 76 mg/liter silver. The silver metabolism was apparently altered because higher silver concentrations were found in the liver. When the diets were made adequate in vitamine E (100 I.U./kg) as well as selenium, the glutahtione peroxidase levels in liver, erythrocytes, and kidney of rats given 751 mg/liter silver in water were 5 percent, 37 percent and 38 percent respectively, of those of control rats (Wagner, et al. 1975, and Swanson, et al. 1974).

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* The case in-based diet itself contained 0.000002 percent selenium.

Whanger (1976b) found that vanadium and zinc apparently promote the liver necrosis seen in rats deficient in selenium and vitamin E, but not to the degree that silver does. The effect of feeding rats nonsupplemented torula yeast diets containing 0.08 percent silver as the acetate was overcome by 40 times (0.004 percent) the required selenium level or by the accepted level of vitamine E (0.006 percent). Whanger speculated that vitamin E is more critically involved in counteracting silver than selenium. Both mercury and silver decreased selenium absorption and tissue content, but mercury did not affect the deficiency-caused liver necrosis.

In addition to antagonism to selenium and vitamin E, an isolated report (Dodds, et al. 1937) stated that silver reduced the antidiuretic activity of pituitary extract in rats given 2 ug of the extract plus 0.2 ml of a 5 percent solution of silver lactate per 200 g body weight.

Whanger, et al. (1976a) found that feeding ewes low-selenium diets with 0.005 percent silver as the acetate did not significantly affect the incidence of white muscle disease (a selenium-deficiency syndrome) in their lambs but significantly altered the concentrations of the enzymes glutamic-oxalo-acetic transaminase (GOT), creatine phosphokinase (CPK), and lactic dehydrogenase (LDH) in the plasma of the lambs. The relative amounts of plasma GOT for low-selenium, low-selenium plus silver, and low-selenium plus selenium diets were 190:616:44; of CPK, 335:216:32; and LDH, 930:2,694:387. Silver gave higher LDH and GOT concentrations than did arsenic or cobalt.

Higher dietary concentrations of silver were required to produce selenium-vitamin E deficiency in pigs fed an adquate diet. Anorexia, diarrhea, and growth depression appeared in four weanling swine fed a diet adequate in selenium and vitamin E, but containing 0.5 percent silver acetate for 4 weeks. Three of the four pigs died (at 21, 23, or 28 days of the experiment); all had necrotic hepatic lesions; and one had the skeletal muscle and cardiac lesions of selenium-vitamin E deficiency. Pulmonary edema and excessive fluid in the peritoneal, pleural, and pericardial cavities were present. Four pigs fed only 0.2 percent silver acetate for 40 days did not develop any pathological or clinical signs of the deficiency, but the selenium content of the liver was significantly increased (average 0.61 mg/kg wet weight). The lesions and mortality were prevented in two pigs by adding 100 I.U./kg -tocopherol, but selenite was ineffective in two other pigs (Van Vleet, 1976).

McDowell, et al. (1978) found that silver supplementation of 0.02 percent to the low selenium-vitamin E diet* of eight pigs for 8 weeks aggravated deficiency symptoms, lowered the selenium concentration of the blood, and increased the selenium concentration in the liver. The pigs reduced their feed intake when it contained silver. The skeletal muscle and cardiac myopathies and the hepatic necrosis were generally more severe in pigs given silver than in those given arsenic or sulfur. The extent of muscular lesions was indicated in silver-treated pigs by the high serum glutamic-oxaloacetic transaminase. The ornithine carbamyl transferase concentration was higher in the pigs treated by silver than with any other agent.

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* The pigs had been on the deficient diet for 4 weeks before introduction of the silver.

Dam, et al. (1958, cited by Jensen, et al. 1974) found that feeding chicks a diet with 0.002 percent (20 mg/kg diet) silver as the acetate promoted exudative diathesis.

Ganther, et al. (1973) reported that silver at 100 mg/liter in the drinking water of chicks promoted the liver necrosis characteristic of vitamin E and selenium deficiency.

Silver acetate at 1,500 mg/liter in the drinking water of vitamin E-deficient chicks promoted exudative diathesis. Silver was also found to be a pro-hemorrhagic factor (Bunyan, et al. 1968).

Hill and Matrone (1970, see also Hill, et al, 1964) found that silver concentration of 0.01 percent (100 mg/kg) in the diet of chicks reduced growth when the diet was deficient in copper. The mortality in the initial 20 chicks was 25 percent after 4 weeks on a copper-adequate diet compared with 60 percent on a copper-deficient diet. The hemoglobin content of the blood and the elastin content of the aorta was reduced in chicks given a diet with a concentration as low as 0.001 percent (10 mg/kg).

Peterson and Jensen (1975a) obtained results in chicks similar to those described below in turkey poults. Feeding chicks a diet containing 0.09 percent (900 mg/kg) silver as the nitrate for 4 weeks depressed growth, enlarged the heart, and increased mortality. The growth depression was not completely corrected by a concentration of 0.005 percent (50 mg/kg) copper in the diet, but the cardiac enlargement and mortality were prevented. The 0.09 percent silver in the diet reduced copper concentrations from those of the controls in blood, liver, spleen, and brain, but did not significantly affect copper concentrations in the kidney or excreta. (The latter was only a 1-day sample and may not have been representative). However, supplementation of the diet with 0.005 percent copper along with the 0.09 percent silver, brought copper levels to those of the controls in blood, liver (but not fat-free liver), and spleen. Again, the copper content in the kidney was normal, but the concentration in the brain was significantly lower and that in the excreta was more than twice as high. Possibly, copper loss through the kidneys was being promoted by silver. Silver obviously reduced tissue uptake of copper, but the experiments did not explain whether this was due to interference with copper metabolism or with copper absorption.

When Peterson and Jensen (1975b) performed similar 4-week experiments with chicks fed a 0.09 percent silver diet marginal in vitamin E and selenium, the mortality was mostly due to exudative diathesis. The growth depression and mortality were prevented by including 0.0001 percent (1 mg/kg) selenium or 100 I.U. vitamin E per kilogram to the diet. When the silver-containing diet was supplemented only by 0.15 percent cystine, there were signs of exudative diathesis in 58 percent of the chicks after 15 days and 90 percent mortality after 28 days (49 percent and 83 percent respectively, without added cystine in the diet). Vitamin E was more effective than selenium in reducing the mortality of the cystine-and-silver-fed chicks.

Chicks fed an otherwise normal diet containing 0.0005 percent selenium showed a slower growth rate, and chicks given 0.004 percent selenium for 2 weeks had increased mortality. Either 0.1 percent silver in the diet as the nitrate or copper as the sulfate improved the growth rate and prevented mortality. As shown by experiments with ^{75}Se, silver interfered with selenium absorption (when given orally or i.m.), and allowed accumulation of a nontoxic selenium compound in the tissues, whereas copper provided primarily the latter effect. Presumably, because of their greater water insolubility, these nontoxic compounds are the selenides (Jensen, 1975).

Selenium-vitamin E deficiency symptoms were also induced in 20 ducklings fed an adequate diet supplemented with 0.2 percent silver acetate for 3 weeks. The birds showed anorexia, retarded growth, a reluctance to stand, and eventual fatalities (2 of the 18 ducklings affected) with myopathies in the gizzard, intestine, skeletal muscle, heart, and hydropericardium unless the diet was supplemented by 200 I.U./kd of -tocopherol. Selenium (0.0001 percent) as sodium selenite did not protect against the deficiency symptoms. The liver content of selenium was low in the deficient silver-fed animals, but was increased when the diet was also supplemented with selenium (Van Vleet, 1977).

Peterson, et al. (1973) fed 21 turkey poults a diet containing 0.09 percent silver as silver nitrate for 4 weeks, which significantly reduced body weight gain, hemoglobin, packed cell volume of the blood, and aortic elastin content while significantly increasing the ratio of wet heart weight to body weight. The heart enlargement was due to copper deficiency.* (Copper is part of the enzyme amine oxidase, required for elastin synthesis). Although six of the poults died (28.6 percent mortality) within the next 18 weeks, during which time they no longer received silver, the factors affected by silver nitrate had reverted to normal except for the appearance of the hearts. They were grossly enlarged, blunt at the apex, and showed marked dilation and thinness of the right ventricle.

Extending the report of the studies on turkey poults by Peterson, et al. (1973), Jensen, et al. (1974) found that there was a variable incidence of gizzard musculature degeneration, which was prevented by adding 0.0001 percent selenium or 50 International Units (I.U.) vitamin E per kilogram to the diet. These agents, however, did not affect the macrocytic hyperchromic anemia; but 0.005 percent copper in the diet reversed the anemia as was mentioned above.

Hoekstra (1975) enumerated some of the defects related to selenium deficiency in many animal species: fetal death and resorption; testicular and liver necroses; degeneration of kidney, muscle, and vessels; hemorrhage; and erythrocyte hemolysis. He proposed a metabolic scheme interrelating the effects of glutathione peroxidase and vitamin E as protectors against sulfur-containing amino acids, oxidant stressors, etc.; but the mechanism whereby silver interferes with selenium and glutathione peroxidase was not explained.

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* Jensen, et al. (1974) later reported that giving the poults 0.005 percent copper in the diet reversed silver's effects on growth rate, blood, and cardiac tissue.

Rotruck, et al. (1973) found that there are four selenium atoms per molecule of the enzyme glutathione peroxidase. Noguchi, et al. (1973, both reports cited by Peterson and Jensen, 1975b) advanced the hypothesis that the selenium-containing glutathione peroxidase destroys peroxides and hydroperoxides within the extramitochondrial water-soluble fraction of the capillary cells and that lipid-soluble vitamin E prevents auto-oxidation of the lipds within the membrane* itself. The greater efficiency of vitamin E rather than selenium in curing selenium-vitamin E deficiency symptoms in silver-fed animals may be due to the fact that vitamin E acts directly, whereas selenium must first be synthesized into glutathione peroxidase or its metabolism and/or absorption are directly interfered with by silver (Peterson and Jensen, 1975b).

Teratogenicity

Few associations between silver and birth defects have appeared in the literature and one is apparently erroneous.

Kukizaki (1975) found only weak cytotoxic effects when silver-tin alloy powder was incubated in seawater with fertilized eggs or early embryos of the sea urchin *Hemicentrotus pulcherrimus*. Metallic mercury, on the other hand, was not only very cytotoxic, the embryos were deformed. However, 5 hours after incorporation with the silver-tin alloy into a dental amalgam, even the cytotoxicity almost disappeared.

Silver was among the 54 elements whose salts were tested for toxicity to 4- and 8-day-old chick embryos, by Ridgway and Karnofsky (1952); but it was not among the nine elements (Tl, Cr, Pb, Co, B, As, Rh, Ba, and Se) whose salts produced abnormalities in embryonic development.

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* Alterations to hepatocyte membranes were consistently seen early in silver feeding studies producing liver necrosis (Grasso, et al. 1969).

Robkin, et al. (1973) reported concentrations of silver (determined by neutron activation analysis) in dry liver tissue from 12 anecephalic fetuses (0.75 ± 0.15 mg/kg), nine premature infants (0.68 ± 0.22 mg/kg), 12 fetuses from therapeutic abortions (0.23 ± 0.05 mg/kg), and 14 fetuses from spontaneous abortions (0.21 ± 0.05 mg/kg). Mercury concentrations exhibited a similar pattern. The age of the tissue groups increased in the order of increasing mercury concentrations. The accumulation of mercury with age may have accounted for the differences, not a teratogenic effect. The authors felt more data from large sample sizes were needed to decide whether the silver anomaly was due to a teratogenic effect or was also due to accumulation with age.

Barrie (1976) described two rare cases of fibular aplasia in human infants from mothers whose intrauterine devices had remained in place during pregnancy. One mother had an I.U.D. of German silver (the Grafenburg ring); the other, an I.U.D. of poly(vinyl acetate) containing barium and copper additives (the standard Dalkan shield). Barrie mistakenly stated that the first shield is mainly silver. According to Thrush, et al. (1968), German silver comprises only nickel, copper, and zinc.

Mutagenicity

Demerec, et al. (1951) studied mutational changes in *Escherichia coli* by the method of inducing back-mutations from streptomycin dependence to nondependence. Incubation with silver nitrate solutions of 0.000005 to 0.000100 percent for 3 to 25 hours allowed 4.3 to 84 percent survival of *E. coli* with 2.1 to 8.2 mutants per 10^8 bacteria after incubation compared with 2.3 to 8.6 mutants per 10^8 bacteria for control plates. Only the lowest concentration gave more mutants than were in the controls (4.8 versus 2.3 mutants per 10^8 bacteria). Thus, silver nitrate was deemed nonmutagenic.

Mutations tested for in Micrococcus pyogenes var. aureus strain FDA209 were resistant to penicillin and/or streptomycin. Clark (1953) found that a 0.000001 percent solution of silver nitrate (a concentration that gave the minimum killing action) apparently was not mutagenic in that the solution did not favor formation of antibiotic-resistant mutants in Micrococcus aureus. (In fact, the controls showed more mutants than the test solutions).*

Nishioka (1975) used the method reported in 1972 by Kada, et al. for screening chemical mutagens. The method, named rec-assay, observes differential growth sensitivities to chemicals in wild and recombination-deficient strains of Bacillus subtilis. Chemicals more inhibitory for Rec^- than for Rec^+ cells are suspected mutagens based on their ability to damage DNA. After exposure for 24 hours to 0.05 ml of a 0.05 M silver chloride solution (sic), both Rec^+ and Rec^- cultures showed the same degree of inhibition.

Fox, et al. (1969) had suggested that silver sulfadiazine derived its antimicrobial activity from its ability to react with cellular DNA. Rosenkranz and co-workers had found that it does in vitro, but not in vivo (four publications were cited 1972-1975). McCoy and Rosenkranz (1978) found that silver sulfadiazine had no mutagenic activity in the Ames test, which examines the substance's ability to mutate histidine-requiring strains of Salmonella typhimurium to histidine independence. Although the typhimurium tester strains gave the usual response to known base substitution and frameshift mutagens in plate assays, usually fewer than 19 mutants per plate were observed with silver sulfadiazine. In suspension culture, the antimicrobial activity of silver sulfadiazine (1 mg/liter) was clearly observed; but the relative number of mutants per 100 million viable cells varied little (7.7 to 10.3) with time, whereas another antimicrobial--2-(2,2-dimethylhydrazino)-4,5-nitro-2-furylthiazole--showed definite mutagenic potential, with 394 mutants per 100 million viable cells 80 minutes after addition of 0.5 mg/liter.

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* 90 verus 179 for streptomycin-resistant mutants per million cells. 9 versus 40 for penicillin-resistant mutants per million cells.

Apparently, silver is a normal, if minute, constituent of DNA. Sabbioni and Girardi (1977) found 0.2 mg/kg silver in calf thymus DNA, but 0.015 mg/kg silver was in the blank. Elements present at the same level as silver, up to 1.2 mg/kg, were mercury, selenium, rubidium, and chromium. Elements present at 2 to 1,450 mg/kg were barium (8), manganese (16), iron (11.6), strontium (2.2), and zinc (1,450.

Von Rosen (1954) exposed germinated Pisum seeds with 1-cm-long rootlets to solutions of heavy metal compounds at 20°C and observed that the chromosome-breaking ability of the very active metal ions were in the following (decreasing) order: Tl, Cd, Cu, Os, Hg, Ag, Ti, Ta, Au, Pt, Cr, and Co. The concentration of the silver ions (probably as the nitrate as in Von Rosen, 1957) was of the order 0.0001 M. The ions of silver and gold produced swollen prophase cells, where the chromosomes were visible as long threads but were often greatly fragmented. Von Rosen (1957) remarked that the elements that were radiomimetically active in producing chromosome disturbances were those that can form strong complexes with protein constituents.

Carcinogenicity

Implanted foils and disks and injected colloidal suspensions of metallic silver have been found to produce tumors or hyperplasia in several studies. Yet the investigators almost always qualify their findings by suggesting the effect is due to the particular physical form of the metal, to its being an exogenous irritant, or to its lowering resistance because of the presence of some solubilized silver ions. Some of the literature data are summarized in Table 17. The data included are of uneven quality because a few of the original references have not been located and some listings are from "Substances Which Have Been Tested for Carcinogenicity" (Hartwell, 1951; Thompson, J.E., and Company, 1969; Shubik and Hartwell, 1969).

Furst (Chemical and Engineering News, 1975) in an address to orthopedic surgeons in West Germany stated that on the metals he and others had tested for carcinogenicity, silver, gold, copper, iron, and lead are "benign".

Nothdurft (1958) found no difference in the incidence of sarcoma formation initiated by s.c. or i.p. injections of silver (17-mm diameter round disks) in rats and mice and that initiated by gold, platinum, or ivory. Wistar

*Some of the studies that have been listed in "Substances Which Have Been Tested for Carcinogenicity" were not really carcinogen assays at all. For example, Hanzlik and Presho (1923) inserted 0.53, 0.621, and 1.56 g silver granules in the gizzards of three pigeons and observed weight loss and sickness in the two pigeons receiving the lower doses. They recovered within 18 and 48 days, respectively. There was no histopathological examination of tissues. In another inappropriately included study, O'Connor (1954), supported by the British Empire Cancer Campaign, induced deep necrosis of the colon tissues by anal insertion into mice of silver nitrate crystals. The mucous membranes and muscle were examined for the extent of regeneration.

TABLE 17

Silver Tested for Carcinogenicity

Investigators	Animal	Strain or Type	Sex	Preparation and Dose	Site and Route	Animals with Tumors	Survival	Duration of Experiment
				Silver Nitrate				
Saffiotti & Shubik (1963)	20 mice[a]	Swiss	M	10% in distd. water 2/week for 43 weeks starting 1 week after topical application of 1.5% DMBA (7,12-dimethylbenz(a)anthracene) in mineral oil	Hair-free skin, topical	3 with 8 papillomas[b] (average latent period 19 weeks 0 carcinomas	18 at 10 weeks 13 at 20 weeks	44 weeks
Saffiotti & Shubik (1963)	20 mice[a]	Swiss	M	Same as above, except croton oil was substituted for the first silver nitrate treatment	Hair-free skin, topical	6 with 14 tumors (1 was a carcinoma) (average latent period 21 weeks)	19 at 10 weeks 15 at 20 weeks	44 weeks
Frei & Stephens (1968)	30 mice	Swiss inbred	M	10% in distd. water, 2/week for _ 50 days	Top ears, topical	0[c]	25 survivors	50 days
				Metallic Silver				
McDonald & Huffman (1955) cited in Shubik & Hartwell (1969)	13 rats	Long Evans	M		Implanted in bladder	P		8 weeks
Nothdurft (1955)	Mice			Disks 12 x 0.02 mm 12/animal	Implanted 6 s.c. on back, 4 i.p., 2 s.c. on abdomen	P		≥ 9 to 12 months
Nothdurft (1955)	Rats	Wistar		Disks 17 x 0.02 mm 12/animal	Implanted 6 s.c. on back, 4 i.p., 2 s.c. on abdomen	2 sarcomas		≥9 to 12 months
Nothdurft (1956) cited in Shubik & Hartwell (1969)	84 rats			17-mm disk implanted (8/animal)	s.c.	65 sarcomas		23 months
Oppenheimer, et al. (1956)	25 rats	Wistar	M	2 pieces of foil, 1.5-cm wide	Imbedded, s.c., abdominal wall	14 (32%) (fibrosarcomas at site of imbedding)		275 to 625 days

TABLE 17 (Continued)

Investigators	Animal	Strain or Type	Sex	Preparation and Dose	Site and Route	Animals with Tumors	Survival	Duration of Experiment
Nothdurft (1958)	35 rats	Wistar	M&F	Fragments 1 x 1 x 0.02 mm	s.c.	0	24 at 18th month, 31 at 12th month	At most 33 months
Schmahl & Steinhoff (1960)	31 rats	BD		Colloidal silver suspension 1.75 mg. 4/week for 10 months then 2.5 mg/week for 7 months. Total dose 65 mg/rat	i.v. or s.c. injections	One spindle-cell sarcoma at injection site at 16 months. Later 8/26 (31%): 6 sarcomas, leukemia, and a laminar epithelial carcinoma. (Average latent period 695 ± 150 days).	(31%)d/	17 months
Becker, et al. (1966)	Rats			Platelets 11 mm x 3 mm thick	Implant	Malignancies at ≥ 295 days		> 295 days
Furst & Schlauder (1977)	Rats	Fischer-344		Fine powder (-300 mesh) in suspension in trioctanoin	s.c.	0e/		

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a/ Fifty female mice given only a similar initiating treating lived 20 to 140 weeks without developing tumors. Among control groups from the same colony, one of 240 females observed for their lifespan developed a papilloma that regressed; and of 240 males, there developed one skin papilloma and a carcinoma of skin appendages. Other control groups totalling 400 mice of both sexes did not develop any tumors within 100 weeks.

b/ The investigators judged silver nitrate to be an agent causing marked epidermal hyperplasia.

c/ John I Thompson and Company (1969), reported that the treatment induced 100% epithelial hyperplasia. It did not. It was therefore, not used in further studies of tumor promotion wherein 1.50% DMBA was used as the carcinogen. In the test described above, the only untoward effect reported was the presence of 17 inflammatory cells after 10 days in a standard area of ear epidermis, compared with three in the controls while the known tumor promoter 50% croton oil caused 176 inflammatory cells.

d/ The rate of spontaneous malignant tumor formation was 1 to 3% in 700 untreated rats.

e/ Rats injected with the vehicle or a suspension of gold powder developed one fibrosarcoma per group. By contrast, 60% of rats injected with cadmium powder developed fibrosarcomas at the injection site.

rats of both sexes treated with pieces of cut-up silver foil (8 s.c. implants in each of 31 to 35 animals); largest particle size (1 x 1 mm) were observed for periods up to a lifetime. Similar implants of gold and platinum were made. After 12 months, there were 31 survivors in the silver group 28, in the gold group; and 26, in the platinum group. The number of survivors after 18 months were 24, 19, and 20, respectively. One rat from each group was observed for 29 months. The last animal to die (at 33 months) had been treated with silver. None of the rats developed sarcomas.

Oppenheimer, et al. (1956) imbedded two 1.5-cm circles or squares of silver foil s.c. into the abdominal wall of each of 25 male Wistar rats immediately ventral to the fascia on either side. The latent period of tumor formation (all fibrosarcomas) in 14 of the rats (32 percent) was 275 to 625 days. The authors had earlier shown that the physical form of plastics played a role in carcinogencity, implants of plain plastics causing many more tumors than perforated film, fibers, or powders. The effect of smoothness may be operative also with metal implants since flexible steel, tantalum, and vitallium foils also produced tumors, in identical experiments, and crumbly tin foil did not. (There were no controls).

Silver alloys were not considered in Table 17 because of the uncertainty of attributing any effect solely to silver. Fujita (1971) imbedded a solid 1-cm^2 plate of a dental silver-palladium-gold alloy s.c. in rats and found tumors (fibrosarcomas, fibroadenomas, and fibromas) in 7 of 14 animals. The incidence of tumors was only 1 in 13 when the plate was perforated.

However, in another study, implanted smooth pellets of a silver-based dental alloy* or pure gold for 5 to 90 days in the oral submucous membranes of rabbits and in the liver, testes, and femoral muscles of rats, were judged to be rather innocuous. The implants produced proliferation of connective tissue and a release of neutrocytes, monocytes, and histiocytes as the primary effects and secondarily produced fibroblasts. The effects of the implants in the rabbits were judged to be mild. Spermatogenesis was noted in the degenerative seminiferous tubules among the proliferated fibrotic stroma surrounding the alloy pellets. In the muscle, new connective tissue invaded the fiber bundles (Habu, 1968).

Both colloidal silver and silver nitrate have been reported to promote tumor growth. Intratumoral injections of colloidal silver in 40 rats appeared to stimulate cancer growth rather than inhibit it as did similar injections of colloidal platinum. In only one of the treated rats (2.5 percent) did the tumor heal compared with 5 of the 30 control rats (16.6 percent). (Colloidal platinum injections in 342 rats had given 14.0 to 50.0 percent healing compared with 0 to 38.0 percent healing in the controls) (Guyer and Mohs, 1933).

Four rats were given s.c. injections of colloidal silver on one side and colloidal platinum on the other. After 2 hours, the metals in the subcutaneous tissues were surrounded by profuse serous exudates and beginning leukocyte invasion. At 24 hours, both metals had induced a beginning fibroblastic proliferation, which replaced the leukocytic exudation almost completely by 48 hours. Colloidal platinum induced a thicker, denser fibroblastic capsule, which may explain its inhibitive effect on cancers by walling them off and diminishing the oxygen supply. Irritant ionic silver was probably present because of the presence of a discoloration in the nearby tissue fluids by 24 hours, and degeneration of the adjacent striated muscle. The foreign body reaction around platinum particles was not accompanied by injury to normal tissue. Possibly, the promotion, by silver, of cancer growth is due to the production of an area of lowered tissue resistance that allows resistant cancer cells to grow freely (Guyer and Mohs, 1933).

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* 70.02 percent silver, 24.70 percent palladium, 5.23 percent gold, and 0.03 percent copper.

Schmahl and Steinhoff (1960) induced tumors in rats with i.v. and s.c. injections of colloidal gold* or colloidal silver. (The LD_{50} for i.v. administration of colloidal silver in rats is 67 mg/kg. (The animals died within 20 to 24 hours with severe pulmonary edema)). They administered 1.75 mg silver to 31 BD-strain rats for the first dose, which was followed at weekly intervals by 2.45 mg s.c. doses so that the total dose per animal over the 10-month period was 44 mg. The group was then given 2.5 mg weekly dose i.v. for 7 months for an additional total dose of 65 mg Ag per rat. Argyria was noticeable in the skin and mucous membranes after 6 to 8 weeks, but their health and growth were not affected. Sixteen months after the start of the injections, one rat developed a spindle-cell sarcoma at the injection site. There were only 26 survivors at this time. Seven others later developed malignant tumors. Altogether, six sarcomas occurred at the injection site. Leukemia and lamellar epithelial carcinoma at the maxillary angle were also observed. The frequency of occurrence of malignancies in the survivors was 8/26 or 31 percent; 23 percent for the local malignancies. The average latent period was 695 ± 150 days. In 700 untreated rats, the rate of spontaneous malignant tumor formation was 1 to 3 percent.

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* Found to be noncarcinogenic.

Saffiotti and Shubik (1963) treated the hair-free skin of 20 male mice with a 1.5 percent solution of the carcinogen DMBA (7,12-dimethylbenz(a)anthracene) in mineral oil. One week later, the mice were treated with a 10 percent aqueous solution of silver nitrate to determine its promoting activity. The silver nitrate solution was applied twice weekly throughout the rest of the 44-week experiment. At 10 weeks, there were 18 survivors; at 20 weeks, 13. Three mice developed eight papillomas (but no carcinomas) with an average latent period of 19 weeks. Silver nitrate was judged to be an agent causing marked epidermal hyperplasia. In another 44-week series, where croton oil was substituted for the first silver nitrate treatment, there were 19 survivors at 10 weeks; 15, at 20 weeks. Six mice of 20 developed tumors, one of which was a carcinoma. The average latent period was 21 weeks. Fifty female mice given only a similar initiating treatment lived at least 20 weeks (the test extended for 140 weeks). None of the animals bore tumors. Among control groups from the same colony, one of 240 females observed for their lifespan developed a papilloma that regressed; and of 240 males, there developed one skin papilloma and a carcinoma of skin appendages. Other control groups totaling 400 mice of both sexes did not develop any tumors within 100 weeks.

On the other hand, silver nitrate has been found in at least one study to be a tumor inhibitor. Taylor and Carmichael (1953) studied the effect of metallic salts (mainly chlorides) on the embryo and tumor (C_3H mouse mammary adenocarcinoma) of tumor-bearing eggs and on dba mouse sarcoma transplants in dba mice. When 0.3 mg aqueous $AgNO_3$ was injected into the egg membrane (46 eggs), survival (at 3 days) was 91 percent that of the controls; tumor weight, 79 percent; and embryo weight, 98 percent. Five consecutive daily subdermal injections of 1.0 mg silver nitrate in saline given to 14 dba mice bearing sarcomas in the inguinal area reduced the tumor size to 65 percent that of the controls (given only saline injections) at 7 days, but reduced the body weight of the mice to only 96 percent. Silver nitrate was one of the more effective tumor growth inhibitors (along with the chlorides of Co, Cu, Hg, Ni, Rh, Ti, and Zn).

Although the literature is replete with clinical reports of cases of argyria, the connections between human cancers and silver as a causal agent are very tenuous. The following reports reflect the difficulty of finding even tenuous connections in the literature.

Schulze and Bingas (1968) attributed the formation of a meningioma surrounding a silver clip left from an operation 2 years before to remove an ependymoma in the brain of an 11-year-old girl to its action as a chronic exogenous stimulus. Hormonal changes during puberty caused the frequent recurrences of the ependymoma.

Some cases of esophageal cancer in certain areas of Brazil have been related to the assiduous habit of "drinking mate tea without sugar, in a gourd through a silver straw, at very hot temperature". According to Dantas (1975), the high temperature may be at least partly the cause of the esophageal cancer.

Bell, et al. (1952) reported that accidental incorporation of pieces of silver amalgam into the alveolus or gingiva during dental procedures appear as a grayish-blue macule in the oral mucous membrane. Unless subjected to stress, as when under a denture, they are not tender nor inflammatory. "They closely resemble a blue nevus and have been removed in some cases on suspicion of neoplasm". Under the microscope (low-power) "they at first glance give a strong impression of blue nevus". There was silver pigment in the blood vessels and a sparse sprinkle of histiocytes. "No giant cells, inflammatory infiltrates, or other tissue reactions have been seen."

CRITERION FORMULATION

Existing Guidelines and Standards

Both of the U.S. standards for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused argyria. (See Table 18 on existing standards for silver.) It should be pointed out how the minimum 1 g silver needed to produce argyria was determined. On page 88 of their book, Hill and Pillsbury (1939) stated that only intravenous doses of silver could be used to determine accurately the amount of silver actually taken into the body since the extent of gastrointestinal or mucous membrane absorption was unknown. Silver arsphenamine had been administered I.V. to human patients suffering from syphilis; 19 of them (14 had advanced symptoms of syphilis; 11 had received other heavy metal treatment*) developed argyria. Those patients developing argyria had received total doses of silver ranging from 0.91 g to 7.6 g within 2 to 10 years. The average total dose was 2.3 g silver. (Fourteen of the patients developing argyria were males). The total number of patients that had been treated with silver arsphenamine was not estimated, but they were probably quite numerous.

Until the U.S. Public Health Service Drinking Water Standards of 1962 (U.S. Department of Health, Education and Welfare, 1962), there were no restrictions on silver in drinking water. Neither the World Health Organization International Standards of 1958 nor the European Standards of 1961 set a limit for silver in drinking water (McKee and Wolf, 1963).

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* Hill and Pillsbury (1939) had pointed out that "Generalized pigmentation of the skin resembling that of argyria may be seen following the introduction of various metals, in particular bismuth, arsenic, and gold." Eight of the 19 people had also received bismuth.

The 1976 National Interim Primary Drinking Water Regulations (U.S. EPA, 1976) included a section on silver that is practically identical to the 1962 Drinking Water Standards (U.S. Department of Health, Education and Welfare, 1962). Both begin, "The need to set a water standard for silver (Ag) arises from its intentional addition to waters for disinfection". Both state, ". . . the amount of silver from injected Ag-arsphenamine, which produces argyria, is precisely known. This value is any amount greater than 1 g of silver, 8 g Ag-arsphenamine". The condition to be avoided was argyria. The phraseology "any amount" is misleading, since probably hundreds of patients over at least 2 decades of this treatment for syphilis had received total doses of silver greater than 0.91 g (Hill and Pillsbury, 1939). The two documents acknowledge, however, that there is "considerable variability in predisposition to argyria", which is clearly seen upon examination of Hill and Pillsbury's report of a few hundred case histories from the literature.

The 1976 document omits the calculations from the 1962 document: "Assuming that all silver ingested is deposited in the integument, it is readily calculated that 10 µg/liters could be ingested for a lifetime before 1 g silver is attained from 2 liters water intake per day; 50 µg/liters silver could be ingested approximately 27 years without exceeding silver deposition of 1 g". Yet, both also consider that intake from foods is "60 to 80 µg/day", based on the balance study of Kehoe, et al. (1940), and that silver would be increased in sulfur-containing foods by combination with silver in the cooking water.

The National Academy of Sciences (1977) in Drinking Water and Health made a somewhat different calculation:

"the interim drinking water level of 50 ug/liter would be equivalent to a retention of 50 ug of silver per day (on the assumption that 50 percent of the intake is retained in the body), and would result in an accumulation of 1 g in 55 years, to give a probable borderline argyria".

The U.S. National Aeronautics and Space Administration recommended silver at 100 ug/liter for safely providing pure drinking water on space flights; Swiss health officials, 200 ug/liter; and German health officials, 100 ug/liter (Silver Institute, 1975).

Maximum contaminant levels for inorganic chemicals in the 1975 National Interim Primary Drinking Water Regulations (40 FR 59565) are based on an average consumption of 2 liters of water per day.

Current Levels of Exposure

Estimates of silver in human diets have varied widely -- from an average of 0.4 ug/day for three Italian populations (Clemente, et al. 1977) to 27 ± 17 ug/day (excluding water) in the United Kingdom (Hamilton and Minski, 1972/1973) to 35 ug/day ([a]man) and 40 ug/day ([a]woman) (Tipton, et al. 1966), and 88 ug/day (Kehoe, et al. 1940). Snyder, et al. (1975) estimated the average intake of silver by Reference man to be 70 ug/day based on a review of the literature. Some of these estimates were based on intake of both food and water. An estimate of 30 ug/day for the average human intake in food is reasonable.

Ambient air levels of silver up to 10.5 ng/m^3 would lead to intake of up to 0.24 ug silver per day (at 23 m^3

Existing Standards Regarding Silver

Medium	Silver Concentration	Authority
Drinking water	50 µg/l	U.S. EPA, (1976); National Academy of Sciences (1977)
Drinking water	0.5 µg/l	State of Illinois (cited in National Academy of Sciences, 1977)
Drinking water	10 µg/l	State of California (cited in National Academy of Sciences)
Workplace air, threshold limit value, 8-hour time-weighted	0.01 mg/m^3	Occupational Safety and Health Administration (1974) (39 FR 23541)
Short-term exposure limit ($\underline{7}$ 15 minutes) 4 times per day)	0.03 mg/m^3	American Conference of Governmental Industrial Hygienists (1977)

respired air per 24 hour period). Exposure from cigarettes is negligible.

An average value for silver ingestion by water intake cannot be made. Silver was detected in only 6.1 percent of 380 finished waters (and in only 6.6 percent of U.S. surface waters). Because of the recent increase of interest in water purification by silver in the United States, many people are probably ingesting water from nonpublic potable water sources at the 1962 drinking water limit of 0.05 mg/liter. Shorter exposure of the U.S. population to European limits might occur during travel by plane or ship.

A diet high in seafood taken from silver-polluted water may increase daily silver consumption. Organisms serving as food for high trophic level aquatic species concentrate silver by a factor of about 200 (brown algae, 240; diatoms, 210). Other concentration factors in higher organisms of the food chain are mussels, 330; scallops, 2,300; oysters, 18,700; and North Sea marine organisms, average 22,000 (Cooper and Jolly, 1969). Thus, regular ingestion of fish, etc., from contaminated water might significantly increase silver dietary intake.

In the workplace, daily intake in the United States is limited to 100 µg/day (0.01 mg/m^3 x 10 m/^{3} per workday). Ground-based cloud-seeding generator operators, however, are exposed to air concentrations exceeding the maximum permissible concentration for several hours at a time.

Special Groups at Risk

People treated with silver-containing medicinals are most at risk of developing argyria, as demonstrated by Hill and Pillsbury (1939) who summarized 357 recorded cases of argyria, 89 percent of which were due to therapeutic use of silver. In the period 1931 to 1939, when more people were exposed to therapeutic forms of silver than in any previous period, 92 percent of the cases were due to medicinals. Cases of occupationally-caused argyria are seldom encountered in the recent literature and were usually diagnosed at least 30 years ago. Hobbyists (e.g., jewelry makers, photograph developers) may not be aware of the precautions needed with silver and may be more at risk of argyria.

There are large individual variations in silver absorption, retention, eliminations, and/or susceptibility to argyria. Although intravenous administration of a total of 0.91 to 7.6 g (average 2.3 g) silver as silver arsphenamine for 2 to 10 years has caused argyria, hundreds of patients have received up to 1.7 g silver I.V. as silver arsphenamine without developing argyria (Cooper and Jolly, 1969; Hill and Pillsbury, 1939).

Over 10,000 cases of burn and leg ulcer patients have been treated with silver medicinals. No cases of argyria have been reported, even when 0.5 percent silver nitrate was used and systemic absorption was shown.

Aside from argyria, more subtle effects may be due to silver ingestion. On the basis of animal experiments, people marginally deficient or deficient in copper, selenium, or Vitamin E may have their deficiency symptoms exacerbated. But rat studies did not support this suggestion. The possibility that silver might render iodine unavailable in regions that otherwise might have just enough iodine to prevent goiter is another suggested consequence of silver in drinking water (Boissevain and Drea 1936). To support the contention, however, elevated silver concentrations had been found in the water of endemic goiter regions such as the western slopes of the Colorado mountains (Boissevain and Drea, 1936).

Basis and Derivation of Criterion

None of the carcinogenicity studies mentioned in the document are acceptable for extrapolation to drinking water by use of the linear, non-threshold model (See Methodology Document). No study demonstrating carcinogenicity of silver has met all of the criteria described in 40 CFR 162.11 (a) ii, A or 43 Fr 163.83-2bc regarding appropriate route, chemical form, number of animals, histologic examination of organs and all obvious lesions, concurrently run control group, etc.

> Data on Human Effects: Although numerous references to the health effects of silver on humans are available, relatively little toxicological or epidemiological data have been reported in the past 30 years. The primary health effect reported is argyria, the unsightly blue-gray discoloration of the skin (and other organs) that develops after repeated exposures to silver compounds. (It is rarely seen today). The current drinking water standard of 50 ug/l was designed to protect against argyria.

Extrapolations from Animal Data: In ten experiments on chronic ingestion by a limited number of rats (rabbits included in one study) of drinking water containing 50 to 20,000 ug/l silver ions,effects were not observed in rats ingesting silver at less than 400 ug/l (See Summary of Pertinent Data). However,in four studies, some physiological effect (as described in Summary of Pertinent Data) was noted at 400 or 500 ug/l

SUMMARY OF PERTINENT DATA

Toxic Effects in Rats Chronically Exposed to Silver in Their Drinking Water

Silver Concentration (ug/liter)	Duration (months)	Effect	Reference
500	6-12	Increase in brain nucleic acids	Kharchenko, et al. (1973b)
2,000	12	Greater increase in brain nucleic acids	
200	8	O	Savluk (1973)
2,000	8	Immunosuppression	
200	3	O	Savluk and Moroz (1973)
20,000	3	Serum protein changes	
400	Not given	O	Just and Szni[illegible] (1936)
400	Not given	Kidney hemorrhage	
700	Not given	More pronounced kidney changes	
1,000	Not given	Kidney, spleen, and liver changes	
50	5	O	Maslenko (1976)
20,000	5	Liver enzyme function change Growth depression by 36% Morphological changes in stomach, small intestine, and liver	
100	6	O	Pak and P[illegible]tina (1973)
20,000	6	Serum SH group depletion	
500	6	O	Karchenko and Stepanenko (1972); Kul'skii, et al. (1972)
2,000	6	Dose-related suppression of conditioned reflex	
20,000	6		
50	11	O	Barkov & El'piner (1968)
500	11	Conditioned reflex change	
5,000	11	Pathological changes in tissues, lowering of immunological activity (changes also seen in rabbits)	
200	8	O	
500	8	Dose-related suppression	Zapadnyuk, et al. (1973)
2,000	8	of conditioned reflex	
2,000			

of silver. Thus, for the purpose of developing a criterion for silver based on animal studies of reasonable quality, the following calculation may be made:

$$\frac{(0.2\ \text{mg/l})\ (0.035\ \text{l/day*})}{0.3\ \text{kg**}} = 0.023\ \text{mg/kg/day}$$

$$0.023\ \text{mg/kg/day} \times 70\ \text{kg/adult human male} = 1.6\ \text{mg/day}$$

* Estimated volume of water consumed by rats.

** Estimated weight of one rat.

A safety factor of 10 to 100 is indicated here, based on several factors:

The National Academy of Sciences guidelines (NAS, Drinking Water and Health, 1977 pp. 803-4): Some valid experimental results are available for prolonged human ingestion with no indication of carcinogenicity, but data are less than complete.

The water consumption rate for rats is considerably higher than that for humans on equivalent body weight basis.

The retention rate of silver in humans versus that in rats is uncertain.

While silver has not been found to be carcinogenic by normal intake routes some evidence exists that it may have carcinogenic activity when implanted as a solid or have activity as a promoter for other carcinogens.

Application of a safety factor of 100 yields a concentration of 8 ug/l, i.e.

$$\frac{1.6\ \text{mg/day}}{(100)\ 2\ \text{L}} = \frac{0.016\ \text{mg/day}}{2\text{L}} = 0.008\ \text{mg/l} = 8\ \text{ug/l}$$

Because of the inherent uncertainties in such a calculation, a value of 10 ug/l silver in water is chosen as the criterion level for protection of human health.

Silver was detectable (>0.1 ug/l) in 104 of 1577 samples taken from 130 points in well and surface waters of the United States. The concentration in positive samples ranged from 0.1-38 ug/l with a median of 2.6 ug/l (Kopp, 1969). Silver concentrations in finished water in public water supplies were about 2.3 ug/l (Durfor and Becker, 1964, and Kopp 1969) with maximum of about 6.0 ug/l while the maximum detected in tap water supplies (2,595 samples) was 30 ug/l (Taylor, 1969).

Silver has been added in special applications to drinking water supplies at higher concentrations (up to 200 ug/l) as a disinfectant, but this method is not economically competitive for large public water supplies.

Some consideration should be given to allowing higher silver concentrations on a short-term or limited basis.

Based on the available data for health effects for ingested silver in humans and animals, the reported levels of silver in foods and in some natural waters, and on its use as a disinfectant in some drinking water, a concentration of 10 ug/l has been calculated to be an acceptable maximum level for public water supplies for protection of human health.

REFERENCES

Albright, C.G., et al. 1967. Development of an electrolytic silver-ion generator for water sterilization in Apollo spacecraft water systems. Apollo applications program. Final report. Abstr. in Star, 7, Feb. 23, 1969.

American Conference of Governmental Industrial Hygienists. 1971. Documentation of the threshold limit values for substances in workroom air, 3rd ed. Am. Conf. Govt. Ind. Hyg., Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists, 1977 TLV Airborne Contaminants Committee. 1977. TLVs^{R} threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1977. Am. Conf. Govt. Ind. Hyg., Cincinnati, Ohio.

Anania, T.L., and J.A. Seta. 1973. Industrial hygiene survey report. United States mint, San Francisco, Calif. Natl. Inst. Occup. Safety and Health. n.p.

Andelman, J.B. 1973. Incidence, variability and controlling factors for trace elements in natural, fresh waters. In: P.C. Singer, ed. Trace metals and metal-organic interactions in natural waters. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.

Andren, A.W., et al. 1974. 4. Ecological research. In: W. Fulkerson, W.D. Schults, and R.I. Van Hook, eds. Ecology and analysis of trace contaminants. Progress report October, 1973 - September, 1974. Oak Ridge Natl. Lab., Oak Ridge, Tenn. p. 61.

Anghileri, L.J. 1968. In vivo and in vitro deiodination of silver iodide. Experientia 24: 895.

Anghileri, L.J. 1969. In vivo breakdown of insoluble halides. Acta Isotop. 9: 347.

Anspaugh, L.R., et al. 1971. Compilation of published information on elemental concentrations in human organs in both normal and diseasd states. 2. Data summary ordered by atomic number, subordered by organ, suborgan, and general health state. Lawrence Livermore Lab., Univ. Calif., Livermore, Calif., UCRL-51013 Pt. 2. Natl. Tech. Inf. Serv., Springfield, Va.

Aponte, G.E. 1973. Some current concepts of the pneumoconioses. Ann. Clin. Lab. Sci. 3: 219.

Armour Research Foundation. 1952. Spectrographic study of meats for mineral-element content. Final report for National Livestock and Meat Board, Armour Research Foundation of Illinois Institute of Technology, Chicago, Ill.

Bader, K.F. 1966. Organ deposition of silver following silver nitrate therapy of burns. Plast. Reconstr. Surg. 37: 550.

Bala, Yu., et al. 1969. Age level of trace elements in the human body. Tr., Voronezh. Gos. Med. Inst. 64: 37; Chem. Abstr. 1970. 13: 96263u.

Bard, C.C., et al. 1976. Silver in photoprocessing effluents. Jour. Water Pollut. Control Fed. 48: 389.

Bargman, R.D., and W.F. Garber. 1973. The control and removal of materials of ecological importance from wastewaters in Los Angeles, California, USA. In: S.H. Jenkins, ed. Advances in water pollution research. Proc. Sixth Int. Conf. in Jerusalem, June 18-23, 1972. Pergamon Press, New York, N.Y. p. 773.

Barkov, G.D., and L.I. El'piner. 1968. O neobkhodimosti ogranicheniya kolichestva serebra v pit'evoi vode (The need for limiting the silver content of drinking water). Gig. Sanit. 33(6): 16.

Barrie, H. 1976. Congenital malformation associated with intrauterine contraceptive device. Br. Med. Jour. 1: 488.

Barsegyants, L.O. 1967. Differentsirovaniye vydelenii chelovecheskogo organizma putem emissionnogo spectral'nogo analiza (Discrimination of human excretions by emission spectrography). Sudebno-Med. Ekspertiza, Min. Zdravookhr. SSSR 10: 30; Chem. Abstr. 1968. 68: 5533.

Becker, T., et al. 1967. Behavior of metallic foreign bodies in animals. Wiss. Chir.-Tag. Deut. Demokrat. Repub., 6th 2: 1722; Chem. Abstr. 1969. 70: 76383t.

Bell, C.D., et al. 1952. Amalgam tattoo-localized argyria. Am. Med. Assoc. Derm. Syph. 66: 523.

Bienvenu, P., et al. 1963. Toxicite generale comparee des ions metalliques. Relation avec la classification periodique (General comparative toxicity of the metallic ions. Relation with the periodic classification). Compt. Rend. 256: 1043.

Bogen, J. 1974. Trace element concentratins in atmospheric aerosols and rainwater, measured by neutron activation and -ray spectrometry. In: Comparative studies of food and environmental contamination. Proc. of a Symp. on Nucl. Techniques in Compar. Stud. of Food and Environ. Contam., Otaniemi, Finland, August 27-31, 1973. Int. Atomic Energy Agency, Vienna, Austria. p. 75.

Boissevain, C.H., and W.F. Drea. 1936. Relation between the occurrence of endemic goiter and the presence of traces of silver and barium in drinking water. Endocrinology 26: 686.

Bondoc, C.C., et al. 1966. Metabolic effects of 0.5 percent silver nitrate therapy for extensive burns in children. Surg. Forum 17: 475.

Bowen, H.J.M. 1966. Trace elements in biochemistry. Academic Press Inc., New York, N.Y.

Boyle, R.W. 1968. Geochemistry of silver and its deposits with notes on geochemical prospecting for the element. Geol. Surv. Can., Bull. No. 160. p. 1.

Bradford, G.R. 1971. Trace elements in the water resources of California. Hilgardia 41: 45.

Bradford, G.R., et al. 1968. Trace and major element content of 170 High Sierra lakes in California. Limnol. Oceanog. 13: 526.

Braidech, M.M., and F.H. Emery. 1935. The spectrographic determination of minor chemical constituents in various water supplies in the United States. Jour. Am. Water Works Assoc. 27: 557.

Brar, S.S., et al. 1970. Instrumental analysis for trace elements present in Chicago area surface air. Jour. Geophys. Res. 75: 2939.

Bruland, K.W., et al. 1974. History of metal pollution in southern California coastal zone. Environ. Sci. Technol. 8: 425.

Buckley, W.R. 1963. Localized argyria. I. Chemical nature of the silver containing particles. Arch. Dermatol. 88:531.

Buckley, W.R., and C.J. Terhaar. 1973. The skin as an excretory organ in argyria. Trans. St. Johns Hosp. Dermatol. Soc. 59: 39.

Buckley, W.R., et al. 1965. Localized argyria. II. Chemical nature of the silver containing particles. Arch. Dermatol. 92: 697.

Bunyan, J., et al. 1968. Vitamin E and stress. VIII. Nutritional effects of dietary stress with silver in vitamin E-deficient chicks and rats. Br. Jour. Nutr. 22: 165.

Burke, J. 1973. Silver sulfadiazine cream in the treatment of burns. Aust. Jour. Hosp. Pharm. 3: 147.

Burton, R.M. 1970. The case of the mysterious tattoo. Jour. Dent. Child. 34: 114.

Camner, P., et al. 1974. Alveolar macrophages and 5 um particles coated with different metals. Arch. Environ. Health 29: 211.

Camner, P., et al. 1977. Lung clearance of 4-mum particles coated with silver, carbon, or beryllium. Arch. Environ. Health 32: 58.

Chemical and Engineering News. 1975. Screening of metal implants urged. Chem. Eng. News 53: 20.

Chusid, J.G., and L.M. Kopeloff. 1962. Epileptogenic effects of pure metals implanted in motor cortex of monkeys. Jour. Appl. Physiol. 17: 697.

Clark, J. 1953. The mutagenic action of various chemicals on Micrococcus aureus. Proc. Okla. Acad. Sci. 34: 114.

Clemente, G.F., et al. 1977. Trace element intake and excretion in the Italian population. Jour. Radioanal. Chem. 37: 549.

Constable, J.D., et al. 1967. Absorption pattern of silver nitrate from open wounds. Plast. Reconstr. Surg. 39: 342.

Cooper, C.F., and W.C. Jolly. 1969. Ecological effects of weather modification: a problem analysis. School of Natural Resour., Univ. Mich., Ann Arbor, Mich.

Cooper, C.F., and W.C. Jolly. 1970. Ecological effects of silver iodide and other weather modification agents: a review. Water Resour. Res. 6: 88.

Creasey, M., and D.B. Moffat. 1973. The deposition of ingested silver in the rat kidney at different ages. Experientia 29: 326.

Curtin, G.C., et al. 1974/75. Movement of elements into the atmosphere from coniferous trees in subalpine forests of Colorado and Idaho. Jour. Geochem. Explor. 3-4: 245.

Dams, R., et al. 1971. Quantitative relationships among the trace elements over industrialized n.w. Indiana. Proc. **Symp. Nucl. Technol. Environ. Pollut.** 1970: 139.

Dantas, W. 1975. Etiological and environmental factors (letter). Jour. Am. Med. Assoc. 231: 1338.

Dawson, G.W. 1974. The chemical toxicity of elements. BNWL-1815, UC-70. Battelle Pacific Northwest Lab., Richland, Wash.

Dawson, R.F. 1974. Basaltic ash as an agricultural substratum in Guatemala. Presented at the 8th Annu. Conf. on Trace Substances in Environ. Health, Univ. Mo., Columbia, Mo., June 11-13. Conf. Abstr. p. 24.

Day, W.A., et al. 1976. Silver deposition in mouse glomeruli. Pathology 8: 201.

Demerec, M., et al. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Nat. 85: 119.

Dequidt, J., et al. 1974. Etude toxicologique experimentale de quelques derives argentiques. 1. Localisation et elimination (Experimental toxicologic study of some silver derivatives. 1. Localization and elimination). Bull. Soc. Pharm. Lille 1: 23.

Diplock, A.T., et al. 1967. Vitamin E and stress. III. The metabolism of D- -tocopherol in the rat under dietary stress with silver. Br. Jour. Nutr. 21: 115.

Diplock, A.T., et al. 1971. The effect of vitamin E on the oxidation state of selenium in rat liver. Biochem. Jour. 123: 721.

Dodds, E.C., et al. 1937. Prolongation of action of the pituitary antidiuretic substances and of histamine by metallic salts. Lancet 2: 309.

Dreisbach, R.H. 1963. Handbook of poisoning, 4th ed. Lange Medical Publications, Los Altos, Calif.

Dulka, J.J., and T.H. Risby. 1976. Ultratrace metals in some environmental and biological systems. Anal. Chem. 48: 640.

Durfor, C.N., and E. Becker. 1962. Public water supplies of the 100 largest cities in the United States, 1962. U.S. Geol. Surv. Water Supply Paper 1812, U.S. Dep. Inter., U.S. Govt. Print. Off., Washington, D.C.

Durum, W.H., and J. Haffty. 1961. Occurrence of minor elements in water. Geol. Surv. Circular 445, Washington, D.C.

Dutkiewicz, T., et al. 1978. Trace element content of human hair determined using neutron activation analysis as monitor of exposure effects to environmental metals. Chem. Anal. (Warsaw) 23: 261.

Dymond, A.M., et al. 1970. Brain tissue reactions to some chronically implanted metals. Jour. Neurosurg. 33: 574.

Enders, A., and A. Moench. 1956. Silberelimination im Organismus bei experimenteller Argyrie (Silver elimination in experimental argyria). Arch. Exp. Pathol. u. Pharmakol. 229: 16; Biol. Abstr. 1957. 40: 3966.

Fedotov, D.D., et al. 1968. Effect of silver ions on the threshold of electroconvulsions. Tr. Gos. Nauch.-Issled. Inst. Psikhiat. 52: 281; Chem. Abstr. 1969. 71: 2016z.

Feller, I., et al. 1976. Baseline results of therapy for burned patients. Jour. Am. Med. Assoc. 236: 1943.

Fleagle, R.G., et al. 1974. Weather modification in the public interest. Am. Meteorol. Soc. and University of Washington Press, Seattle, Wash.

Fox, C.L., Jr. 1973. use of silver sulfadiazine in burned patients. In: J.B. Lynch and S.R. Lewis, eds. Symposium on the treatment of burns. C.V. Mosby Co., St. Louis, Mo. p. 123.

Fox, C.L., Jr. 1975. Silver sulfadiazine for control of burn wound infections. Int. Surg. 60: 275.

Fox, C.L., et al. 1969. Control of Pseudomonas infection in burns by silver sulfadiazine. Surg. Gynecol. Obstet. 128: 1021.

Frank, R.H., Jr. 1969. Trace metal pollution of the lower North Canadian River basin. Ph.D. dissertation, Univ. Okla. (Xerox University Microfilms, Ann Arbor, Mich.)

Frei, J.V., and P. Stephens. 1968. The correlation of promotion of tumor growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br. Jour. Cancer 22: 83.

Fujita, S. 1971. Silver-palladium-gold alloys carcinogenicity and acid mucopolysaccharides in the induced tumors. Shika Igaku 34: 918; Chem. Abstr. 1972. 77: 136075a.

Furchner, J.E., and G.A. Drake. 1968. A radiation protection guide for silver-110 estimated from retention in small mammals. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3848-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 90.

Furchner, J.E., et al. 1966a. Retention of silver-110 by mice. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3610-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 186.

Furchner, J.E., et al. 1966b. Effective retention of silver-110 by dogs after oral administration. Annu. Rep. Biol. and Med. Res. Group (H-4) of the Health Div. LA-3610-MS. U.S. AEC Univ. Calif. Los Alamos Sci. Lab. p. 191.

Furchner, J.E., et al. 1968. Comparative metabolism of radionuclides in mammals. IV. Retention of silver-110m in the mouse, rat, monkey, and dog. Health Phys. 15: 505.

Furst, A., and M.C. Schlauder. 1977. Inactivity of two noble metals as carcinogens. Jour. Environ. Pathol. Toxicol. 1: 51.

Gafafer, W.M., ed. 1964. Occupational diseases, a guide to their recognition. U.S. Dep. Health, Education, and Welfare, Public Health Serv., U.S. Govt. Print. Off., Washington, D.C.

Ganther, H.E., et al. 1973. Protective effects of selenium against heavy metal toxicites. In: D.D. Hemphill, ed. Trace substances in environmental health. VI. Proc. Univ. Mo. 6th Annu. Conf. on Trace Subst. in Environ. Health, June 13-15, 1972. Columbia, Mo. p. 247.

Garner, R.J. 1972. Transfer of radioactive materials from the terrestrial environment to animals and man. CRC Press, Cleveland, Ohio.

Gettler, A.O., et al. 1927. A contribution to the pathology of generalized argyria with a discussion of the fate of silver in the human body. Am. Jour. Pathol. 3: 631.

Grabowski, B.F., and W.G. Haney, Jr. 1972. Characterization of silver deposits in tissue resulting from dermal applicatio of a silver-containing pharmaceutical. Jour. Pharm. Sci. 61: 1488.

Grant, G.C., et al. 1975. Lead, mercury and silver in Chilean mummy tissue. In: Int. conf. on heavy metals in the environ., Toronto, Ontario, Canada, Oct. 27-31, 1975. p. B-72.

Grasso, P., et al. 1969. The role of dietary silver in the production of liver necrosis in vitamin-E-deficient rats. Exp. Mol. Pathol. 11: 186.

Greenberg, R.R., et al. 1978. Composition and size distributions of particles released in refuse incineration. Environ. Sci. Technol. 12: 566.

Guyer, M.F., and F.E. Mohs. 1933. Rat carcinoma and injected colloidal platinum. Arch. Pathol. 15: 796.

Habu, T. 1968. Histopathological effects of silver-palladium-gold alloy implantation on the oral submucous membranes and other organs. Shika Igaku 31: 17; Chem. Abstr. 1968. 69: 95035b.

Ham, K.N., and J.D. Tange. 1972. Silver deposition in rat glomerular basement membrane. Aust. Jour. Exp. Biol. Med. Sci. 50: 423.

Hamilton, E.I., and M.J. Minski. 1972/1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. Sci. Total Environ. 1: 375.

Hamilton, E.I., et al. 1972/1973. The concentrations and distribution of some stable elements in healthy tissues from the United Kingdom. An environmental study. Sci. Total Environ. 1: 341.

Hanzlik, P.J., and E. Presho. 1923. Comparative toxicity of metallic lead and other heavy metals for pigeons. Jour. Pharmacol. Exp. Ther. 21: 145.

Harker, J.M., and D. Hunter. 1935. Occupational argyria. Br. Jour. Dermatol. 47: 441.

Harrison, P. R., et al. 1971. Areawide trace metal concentrations measured by multielement neutron activation analysis. A one day study in northwest Indiana. Jour. Air Pollut. Contro. Assoc. 21: 563.

Hartford, C.E., and S.E. Ziffren. 1972. The use of 0.5 percent silver nitrate in burns: results in 220 patients. Jour. Trauma 12: 682.

Hartwell, J.L. 1951. Survey of compounds which have been tested for carcinogenic activity, 2nd ed. Public Health Serv. Publ. No. 149, Fed. Security Agency, Public Health Serv., U.S. Govt. Print. Off., Washington, D.C.

Hawkes, H.E., and J.S. Webb. 1962. Geochemistry in mineral exploration. Harper and Row Publishers, Inc., New York, N.Y.

Henderson, R.N. 1975. Silver sulfadiazine adverse effects. Am. Jour. Hosp. Pharm. 32: 1103.

Hill, C.H., et al. 1964. Mercury and silver interrelationships with copper. Jour. Nutr. 88: 107.

Hill, W.R., and D.M. Pillsbury. 1939. Argyria, the pharmacology of silver. The Williams and Wilkins Co., Baltimore, Md.

Hoekstra, W.G. 1975. Biochemical function of selenium and its relation to vitamin E. Fed. Proc. 34: 2083.

Hoey, M.J. 1966. The effects of metallic salts on the histology and functioning of the rat testis. Jour. Reprod. Fert. 12: 461.

Hunt, J.S., et al. 1976. Immune complex glomerular disease in argyric mice. Patho-logy 8: 205.

Indraprasit, S., et al. 1974. Tissue composition of major and trace elements in uremia and hypertension. Jour. Chronic Dis. 27: 135.

Jenne, E.A., et al. 1977. Inorganic speciation of silver in natural waters - fresh to marine. Trans. Am. Geophys. Union 58: 1168.

Jenkins, C.E., et al. 1972. Radionuclide distribution in Olympic National Park, Washington. Water, Air, Soil Pollut. 1: 181.

Jensen, L.S. 1975. Modification of selenium toxicity in chicks by dietary silver and copper. Jour. Nutr. 105: 769.

Jensen, L.S., et al. 1974. Inducement of enlarged hearts and muscular dystrophy in turkey poults with dietary silver. Poult. Sci. 53: 57.

Johnstone, R.T., and S.E. Miller. 1960. Occupational diseases and industrial medicine. W.B. Saunders Company, Philadelphia, Penn.

Jones, A.M., and J.A. Bailey. 1974. Effect of silver from cloud seeding on cecal flora of rabbits. Water, Air, Soil Pollut. 3: 353.

Just, J., and A. Szniolis. 1936. Germicidal properties of silver in water. Jour. Am. Water Works Assoc. 28: 492.

Kalistratova, V.S., et al. 1966. Behavior of ^{111}Ag in animals. Raspredel. Biol. Deistvie Radioaktiv Izotop., Sb. Stratei. p. 146; Chem. Abstr. 1967. 67: 51853w.

Karalekas, P.C., et al. 1976. Lead and other trace metals in drinking water in the Boston metropolitan area. Jour. New England Water Works Assoc. 90: 150.

Kehoe, R.A., et al. 1940. A spectrochemical study of the normal ranges of concentration of certain trace metals in biological materials. Jour. Nutr. 19: 579.

Kent, N.L., and R.A. McCance. 1941. The absorption and excretion of 'minor elements' by man. I. Silver, gold, lithium, boron and vanadium. Biochem. Jour. 35: 837.

Kent-Jones, D.W., and A.J. Amos. 1957. Modern cereal chemistry, 5th ed. The Northern Publishing Co., Ltd., Liverpool, England.

Kharchenko, P.D., and P.Z. Stepanenko. 1972. Characteristics of disturbances in albino rat higher nervous activity during the action of silver electrolytic solutions. Fiziol. Zh. Akad. Nauk. Ukr. RSR 18: 596.

Kharchenko, P.D., et al. 1973a. Zmina vmistu nukleinovikh kislot u golovnomu mozku i pechintsi shchuriv pri trivalomu vvedenni ioniv sribla s pitnoyu vodoyu (Change in the nucleic acid level in rat brain and liver during long-term introduction of silver ions with drinking water). Fiziol. Zh. Akad. Nauk. Ukr. RSR 19: 362.

Kharchenko, P.D., et al. 1973b. Izmenenie soderzhaniya nukleinovykh kislot v golovnom mozge pri dlitel'nom vvedenii ionov serebra s pit'evoi vodoi (Change in the nuclein acid content in the brain during long-term administration of silver ions in the drinking water). Vodopodgot. Ochistka Prom. Stokov 10: 91.

Kiker, R.G., et al. 1977. A controlled study of the effects of silver sulfadiazine on white blood cell counts in burned children. Jour. Trauma 17: 835.

Klein, D.A. 1978. Effects on humans. In: D.A. Klein, ed. Environmental impacts of artificial ice nucleating agents. Dowden, Hutchinson, and Ross, Inc., Stroudsburg, Penn. (draft, n.p.)

Klein, D.H. 1972. Mercury and other metals in urban soils. Environ. Sci. Technol. 6: 560.

Konradova, V. 1968a. The ultrastructure of the tracheal epithelium in rabbits following the inhalatin of aerosols of colloidal solutions of heavy metals. 1. Changes in the ultrastructure of the tracheal epithelium after 2-hour inhalatin of colloidal solutions of iron and silver. Folia Morphol. (Praha) 16: 258.

Konradova, V. 1968b. The ultrastructure of the tracheal epithelium in rabbits following the inhalation of aerosols of colloidal solutions of heavy metals. II. Signs of cell alteration in the epithelium after 8 hour inhalatin of colloidal solutions of iron and silver. Folia Morphol. (Praha) 16: 265.

Kopp, J.F. 1969. The occurrence of trace elements in water. In: D.D. Hemphill, ed. Trace substances in environmental health - III. Proc. Univ. Mo. Third Annu. Conf. on Trace Substances in Environ. Health, Univ. Mo., Columbia, Mo., June 24-26, 1969. p. 59.

Kopp, J.F., and R.C. Kroner. 1967. Tracing water pollution with an emission spectrograph. Water Pollut. Contr. Fed. 39: 1660.

Kopp, J.F., and R.C. Kroner. 1970. Trace metals in waters of the United States. U.S. Dep. Inter., Fed. Water Pollut. Contr. Adm., Cincinnati, Ohio.

Kroner, R.C., and J.F. Kopp. 1965. Trace elements in six water systems of the United States. Jour. Am. Water Works Assoc. 57: 150.

Kukizaki, S. 1975. Studies on the effects of dental amalgam upon the fertilization and early development of sea urchin eggs (Hemicentrotus pulcherrimus). Jour. Jap. Soc. Dent. Appar. Mater. 16: 123.

Kul'skii, L.A., et al. 1972. Dinamika zmin korkovoi diya'nosti v bilikh shchuriv pri khronichnyi intoksikatsii sriblom (Dynamics of cortical acitivity changes in albino rats after chronic silver intoxication). Dopov. Akad. Nauk. Ukr. RSR, Ser. B 34: 660.

Kul'skii, L.A., et al. 1973. Disinfection and preservation of water by silver. In: Aktualne vodoprovedeniye sanitarniy mikrobiologii. Med. Acad. USSR, Public Health Water Inst., Moscow, USSR. p. 111; New silver technology. Silver abstracts from the current world literature. 1975. October. p. 11.

Lanford, C. 1969. Effect of trace metals on stream ecology. Paper presented at the Cooling Tower Inst. meeting, Jan. 20, 1969.

La Torraca, F. 1962. Reperti anatomo-isto-patologici ed istochimici nell'intossicazione acuta sperimentale da sali di argento (Anatomic, histopathological, and histochemical aspects of acute experimental intoxication with silver salts). Folia med. (Naples) 45: 1065; Chem. Abstr. 1964. 58: 11883f.

Leirskar, J. 1974. On the mechanism of cytotoxicity of silver and copper amalgams in a cell culture system. Scand. Jour. Dent. Res. 82: 74.

Lever, W. F. 1961. Histopathology of the skin. J.B. Lippincott Co., Philadelphia, Penn.

Lifshits, V.M. 1965. Spectrographic determination of trace elements in fraction of erythrocytes and human plasma. Lab. Delo. p. 655; Chem. Abstr. 1966. 64: 3949b.

Luoma, S.N., and E.A. Jenne. 1977. The availability of sediment-bound cobalt, silver and zinc to a deposit-feeding clam. In: H. Drucker and R.E. Wilding, eds. Biological implications of metals in the environment. Proc. 15th Annu. Hanford Life Sci. Symp. at Richland, Wash., Sept. 29-Oct. 1, 1975. CONF-750929 Natl. Tech. Inf. Serv., Springfield, Va.

Lynch, J.B. 1976. Current status of treatment burns. South. Med. Jour. 69: 1085.

Marks, R. 1966. Contact dermatitis due to silver. Br. Jour. Dermatol. 78: 606.

Marshall, J.P., and R.P. Schneider. 1977. Systemic argyria secondary to topical silver nitrate. Arch. Dermatol. 113: 1077.

Martin, E.W., ed.-in-chief. 1965. Remington's pharmaceutical sciences, 13th ed. Mack Publishing Co., Easton, Penn.

Masironi, R., ed. 1974. Trace elements in relation to cardiovascular diseases. World Health Organ., Geneva, Switzerland.

Maslenko, A.A. 1976. Vliyanie serebyanoi vody i vody konservirovannoi serebrom na organy pishchevareniya (Effect of "silver water" and water preserved with silver on the digestive organs). Vrach. Delo 5: 88.

Mazhbich, B.I. 1961. Some problems in pathogenesis of pulmonary edema provoked by silver nitrate. III. The mechanism of death of experimental animals. Buyll. Eksptl. Biol. i Med. 50: 70; Bull. Exp. Biol. Med. 1961. 50: 821; Chem. Abstr. 1961. 55: 11657c.

McCabe, L.J. 1969. Trace metals content of drinking water from a large system. Presented at the Symp. on Water Qual. in Distr. Systems, Div. of Water, Air, and Waste Chem., Am. Chem. Soc. Natl. Mtg., Minneapolis, Minn., April 13, 1969.

McCabe, L.J. 1970. Metal levels found indistribution samples. Presented at the Am. Water Works Assoc. Seminar on Corrosion by Soft Water, Washington, D.C., June 21, 1970.

McCoy, E.C., and H.S. Rosenkranz. 1978. Silver sulfadiazine: lack of mutagenic activity. Chemotherapy 24: 87.

McDowell, L.R., et al. 1978. Influence of arsenic, sulfur, cadmium, tellurium, silver and selenium on selenium-vitamin-E deficiency in pig. Nutr. Rep. Int. 17: 19.

McKee, J.E., and H.W. Wolf, eds. 1963. Water quality criteria, 2nd ed. Calif. State Water Resour. Contr. Board, Publ. 3-A (Reprint Jan., 1973).

Merritt, W.F. 1971. Identification and measurement of trace elements in fresh water by neutron activation. In: Int. Symp. on Ident. and Measurement of Environ. Pollut., Ottawa, Ontario, Canada, June 14-17, 1971. Natl. Res. Counc. of Canada, Ottawa, Canada. p. 358.

Mischel, W. 1956. Uber die chemische Zusammensetzung der menschlichen Plazenta mit besonderer Berucksichtigung des biogenen Amin Cholin (Chemical composition of the human placenta). Zentr. Gynakol. 78: 1089.

Mitteldorf, A.J., and D.O. Landon. 1952. Spectrochemical determination of the mineral-element content of beef. Anal. Chem. 24: 469.

Moffat, D.B., and M. Creasey. 1972. The distribution of ingested silver in the kidney of the rat and of the rabbit. Acta Anat. 83: 346.

Monafo, W.W., and C.A. Moyer. 1968. The treatment of extensive thermal burns with 0.5 percent silver nitrate solution. Ann. N.Y. Acad. Sci. 150: 937.

Moncrief, J.A. 1974. Topical antibacterial therapy of the burn wound. Clin. Plast. Surg. 1: 563.

Muroma, Ali. 1961. Skin reactions produced by certain metallic salts. Ann. Med. Exp. Biol. Fenniae (Helsinki) 39: 277.

Murthy, G.K., and U. Rhea. 1968. Cadmium and silver content of market milk. Jour. Dairy Sci. 51: 610.

Myers, A.T., et al. 1958. A spectrochemical method for the semiquantitative analysis of rocks, minerals, and ores. U.S. Geol. Surv. Bull. 1084: 207.

Nadkarni, R.A., and W.D. Ehmann. 1969. Determination of trace elements in the reference cigarette tobacco by neutron activation analysis. Radiochem. Radioanal. Lett. 2: 161.

Nadkarni, R.A., et al. 1970. Investigations on the relative transference of trace elements from cigarette tobacco into smoke condensate. Tobacco 170(11): 25.

Nathanson, J.A., and F.E. Bloom. 1976. Heavy metals and adenosine cyclic 3,5-monophosphate metabolism. Possible relevance to heavy metal toxicity. Mol. Pharmacol. 12: 390.

National Academy of Sciences. 1977. Drinking water and health. U.S. Environ. Prot. Agency, Washington, D.C., PB-269 519. Natl. Tech. Inf. Serv., Springfield, Va.

Nelmes, A.J., et al. 1974. The implication of the transfer of trace metals from sewage sludge to man. In: D.D. Hemphill, ed. Trace substances in environmental health - VIII. Proc. Univ. Mo. 8th Annu. Conf. on Trace Substances in Environ. Health. Univ. Mo., Columbia, Mo., June 11-13, 1974. p. 145.

Neri, L.C., et al. 1975. Health aspects of hard and soft waters. Jour. Am. Water Works Assoc. 67: 403.

Nesbitt, R.U., and B.J. Sandmann. 1977. Solubility studies of silver sulfadiazine. Jour. Pharm. Sci. 66: 519.

Newton, D., and A. Holmes. 1966. A case of accidental inhalation of zinc-65 and silver-110m. Radiat. Res. 29: 403.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185.

Noddack, I. and W. Noddack. 1939. Die Haufigkeiten der Schwermetalle in Meerstieren (The frequency of heavy metals in sea organisms.) Arkiv. Zool. 32 A (4): 1.

Nothdurft, H. 1955. Die experimentelle Erzeugung von Sarkomen bei Ratten und Mausen durch Implantation von Rundscheiben aus Gold, Silber, Platin oder Elfenbein (Experimental production of sarcomas in rats and mice by implantation of round disks of gold, silver, platinum, or ivory). Naturwiss. 42: 75.

Nothdurft, H. 1958. Uber die Nichtexistenz von 'Metallkrebs' im Falle der Edelmetalle (The non-existence of metal cancers in the case of noble metals). Naturwiss. 45: 549.

O'Conner, R.J. 1954. The healing of localized areas of necrosis in the colon of the mouse. Br. Jour. Exp. Pathol. 35: 545.

Olcott, C.T. 1948. Experimental argyrosis. IV. Morphological changes in the experimental animal. Am. Jour. Pathol. 24: 813.

Olcott, C.T. 1950. Experimental argyrosis. V. Hypertrophy of the left ventricle of the heart in rats ingesting silver salts. Arch. Pathol. 49: 138.

Oppenheimer, B.S., et al. 1956. Carcinogenic effect of metals in rodents. Cancer Res. 16: 439.

Orentreich, N., and H.H. Pearlstein. 1969. Traumatic tattoo due to silver salt. Arch. Dermatol. (Chicago) 100: 107.

Owens, C.J., et al. 1974. Nephrotic syndrome following topically applied sulfadiazine silver therapy. Arch. Intern. Med. 134: 332.

Page, A.L. 1974. Fate and effects of trace elements in sewage sludge when applied to agricultural lands. A literature review study (review copy). Ultimate Disposal Res. Program, Environ. Prot. Agency, Cincinnati, Ohio.

Pak, Z.P., and V.P. Petina. 1973. Vliyanie serebra na aktivnost'SH-grupp syvorotki krovi belykh krys (Effect of silver on the activity of the sulfhydryl groups of white rat blood serum). Vodopodgot. Ochistka Prom. Stokov 10: 80.

Pariser, R.J. 1978. Generalized argyria. Clinicopathologic features and histochemical studies. Arch. Dermatol. 114: 373.

Peterson, R.P., and L.S. Jensen. 1975a. Interrelationship of dietary silver with copper in the chick. Poult. Sci. 54: 771.

Peterson, R.P., and L.S. Jensen. 1975b. Induced exudative diathesis in chicks by dietary silver. Poult. Sci. 54: 795.

Peterson, R.P., et al. 1973. Effect of silver-induced enlarged hearts during the first four weeks of life on subsequent performance of turkeys. Avian Dis. 17: 802.

Phalen, R.F., and P.E. Morrow. 1973. Experimental inhalation of metallic silver. Health Phys. 24: 509.

Polachek, A.A., et al. 1960. Metabolism of radioactive silver in a patient with carcinoid. Jour. Lab. Clin. Med. 56: 499.

Putzke, H.P. 1967. Experimentelle Argyrose. (Schicksal der Silberablagungen in Leber und Pankreas) Experimental argyrosis. (The fate of silver deposits in liver and pancreas) . Z. Ges. Inn. Med. 22(2): 48.

Ragaini, R.C., et al. 1977. Environmental trace metal contamination in Kellogg, Idaho, near a lead smelting complex. Environ. Sci. Technol. 11: 773.

Rattonetti, A. 1974. Determination of soluble cadmium, lead, silver, and indium in rainwater and stream water with the use of flameless atomic absorption. Anal. Chem. 46: 739.

Reynolds, C.L., Jr., and F.E. Wawner. 1977. Experimental observations on the corrosion of silver-tin (Ag_3Sn) amalgams. Jour. Biomed. Mater. Res. 11: 629.

Ridgway, L.P., and D.A. Karnofsky. 1952. The effects of metals on the chick embryo: Toxicity and production of abnormalities in development. Ann. N.Y. Acad. Sci. 55: 203.

Robkin, M.A., et al. 1973. Trace metal concentrations in human fetal livers. Trans. Am. Nucl. Soc. 17: 97.

Romans, I.B. 1968. Chapter 24. Oligodynamic metals. In: C.A. Lawrence and S.S. Block, eds. Disinfection, sterilization, and preservation. Lea and Febiger, Philadelphia, Penn. p. 372.

Roy, D.R., and J.A. Bailey. 1974. Effect of silver from cloud seeding on rumen microbial function. Water, Air, Soil Pollut. 3: 343.

Sabbioni, E., and F. Girardi. 1977. Metallobiochemistry of heavy metal pollution: nuclear and radiochemical techniques for long term - low level exposure (LLE). Sci. Total Environ. 7: 145.

Saffiotti, U., and P. Shubik. 1963. Studies on promoting action in skin carcinogenesis. Natl. Cancer Inst. Monogr. 10: 489.

Sales Luis, A., and C. Silva Duarte. 1960. Experimental study on the pathogenesis of acute pulmonary edema. I. Pulmonary edema induced by silver nitrate. Mal. Cardiovasc. 1: 39; Chem. Abstr. 1962. 56: 10801g.

Savluk, O.S. 1973. Vliyanie anodnorastvorimogo serebra na retikuloendotelial'nuyu sistemu eksperimental'nykh zhivotnykh (Effect of anodically dissolved silver on the reticuloendothelial system of experimental animals). Vodopodgot. Ochistka Prom. Stokov 10: 72.

Savluk, O.S., and O.G. Moroz. 1973. Reaktsiya organizma belykh krys na dlitel'noe vvedenie serebra s pit'evoi vodoi (Reaction of albino rats to long-term intake of silver with the drinking water). Vodopodgot. Ochistka Prom. Stokov 10: 99.

Sax, N.I. 1963. Silver--silver thioarsenite. In: Dangerous properties of industrial materials, 2nd ed. Reinhold Publishing Corporation, New York, N.Y. p. 1174.

Schelenz, R. 1977. Dietary intake of 25 elements by man estimated by neutron activation analysis. Jour. Radioanal. Chem. 31: 539.

Schmahl, D., and D. Steinhoff. 1960. Versuch zur Krebserzeugung mit kolloidal Silber- und Goldlosungen an Ratten (Experimental carcinogenesis in rats with colloidal silver and gold solutions). Z. Krebsforsch. 63: 586.

Schulze, A., and B. Bingas. 1968. Meningioma development induced by a foreign body. Beitr. Neurochir. 15: 297.

Schwartz, L., et al. 1947. Occupational diseases of the skin. Lea and Febiger, Philadelphia, Penn.

Scott, K.G., and J.G. Hamilton. 1948. The metabolism of silver. Jour. Clin. Invest. 27: 555.

Scott, K.G., and J.G. Hamilton. 1950. The metabolism of silver in the rat with radiosilver used as an indicator. Univ. Calif. (Berkeley) Publ. Pharmacol. 2: 241.

Shaver, S.L., and K.E. Mason. 1951. Impaired tolerance to silver in vitamin E deficient rats. Anat. Rec. 109: 383.

Shaw, E.B. 1977. Questions need for prophylaxis with silver nitrate (letter). Pediatrics 59: 792.

Shouse, S.S., and G.H. Whipple. 1931. Effects of intravenous injection of colloidal silver on haemopoietic system in dogs. Jour. Exp. Med. 53: 413.

Shubik, P., and J.L. Hartwell. 1969. Survey of compounds which have been tested for carcinogenic activity, Supplement 2. Public health Serv. Publ. No. 149, U.S. Dep. Health, Education, and Welfare, U.S. Govt. Print. Off., Washington, D.C.

Sill, C.W., et al. 1964. comparison of excretion analysis with whole-body counting for assessment of internal radioactive contaminants. Health and Safety Div., AEC Accession No. 43318, Rep. No. IDO-12038. U.S. Atomic Energy Comm., Idaho Falls, Ida.

Silver Institute. 1973a. Silver carbon filter purifies swimming pool. Silver Inst. Lett. 3(5): 1.

Silver Institute. 1973b. Silver clears up polluted water. Silver Inst. Lett. 3(7): 3.

Silver Institute. 1973c. Silver Institute board hears of new silver market. Silver Inst. Lett. 3(8): 1.

Silver institute. 1974. Silver purifiers at swimming pool show. Silver inst. Lett. 4(2): 2.

Silver Institute. 1975. Silver guards good health. Silver Inst. Lett. 5(5): 1.

Silver Institute. 1976a. Filters with silver in planes, homes, offices. Silver Inst. Lett. 6(3): 2.

Silver Institute. 1976b. Silver: a $5 insurance policy. Silver Inst. Lett. 6(5): 1.

Silver Institute. 1976c. Tests show silver best water purifier. Silver Inst. Lett. 6(11): 1.

Silver Institute. 1977a. Silver in the healing of burns. Silver Inst. Lett. 7(4): 2.

Silver Institute. 1977b. Silver purifies water on drilling rigs. Silver Inst. Lett. 7(8): 1.

Silver Institute. 1977c. Silver compound saved legs marked for amputation. Silver Inst. Lett. 7(9): 3.

Silver Institute. 1978. In 70 countries silver cleans up polluted water. Silver Inst. Lett. 8(2): 1.

Smith, I.C., and B.L. Carson. 1977. Trace metals in the environment. Vol. 2. Silver. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.

Snyder, W.S., et al. 1975. Report of the task group on reference man. Pergamon Press, Oxford.

Standler, R.C., and B. Vonnegut. 1972. Estimated possible effects of silver iodide cloud seeding on human health. Jour. Appl. Meteorol. 11: 1388.

Stokes, P.M., et al. 1973. Heavy-metal tolerance in algae isolated from contaminated lakes near Sudbury, Ontario. Can. Jour. Bot. 51: 2155.

Strauch, B., et al. 1969a. Methemoglobinemia: a complication of silver nitrate therapy used in burns. AORN Jour. 10(4): 54.

Strauch, B., et al. 1969b. Successful treatment of methemoglobinemia secondary to silver nitrate therapy. New England Jour. Med. 281: 257.

Struempler, A.W. 1975. Trace element composition in atmospheric particulates during 1973 and the summer of 1974 at Chadron, Neb. Environ. Sci. Technol. 9: 1164.

Sunderman, F.W., Jr. 1973. Atomic-absorption spectrometry of trace metals in clinical pathology. Human Pathol. 4: 549.

Swanson, A.B., et al. 1974. Antagonistic effects of silver and tri-o-cresyl phosphate on selenium and glutathione peroxidase in rat liver and erythrocytes. Federation Proc. 33: 693.

Taylor, A., and N. Carmichael. 1953. The effect of metallic chlorides on the growth of tumor and nontumor tissue. Univ. Texas Publ. No. 5314, Biochem. inst. Stud. 5, Cancer Stud. 2. p. 36.

Taylor, F.B. 1971. Trace elements and componds in water. Jour. Am. Water Works Assoc. 63: 728.

Thompson, John I., and Company. 1969. Survey of compounds which have been tested for carcinogenic activity, 1968-1969 volume. DHEW Publ. No. (NIH) 72-35, Public Health Serv. Publ. No. 149. U.S. Dep. Health, Education, and Welfare, Washington, D.C.

Thrush, P.W., et al. 1968. A dictionary of mining, mineral, and related terms. U.S. Dep. Inter., U.S. Govt. Print. Off., Washington, D.C.

Tipton, I.H., and M.J. Cook. 1963. Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys. 9: 103.

Tipton, I.H., and P.L. Stewart. 1970. Long term studies of elemental intake and excretion of three adult male subjects. Dev. Appl. Spectrosc. 8: 40.

Tipton, I.H., et al. 1966. Trace elements in diets and excreta. Health Phys. 12: 1683.

Tong, S.S.C., et al. 1974. Trace metals in Lake Cayuga lake trout (Salvelinus namaycush) in relation to age (brief communication). Jour. Fish. Fes. Board Can. 31: 238.

Toxic Materials News. 1975. EPA finds ocean dumping causing build-up of metals in some Maryland shellfish. Toxic Mater. News 2(3): 24.

Toxic Materials News. 1978. Heavy metals pose no threat to Manassas water supply, Virginia says. Toxic Mater. News 5(1): 4.

Turekian, K.K., and M.R. Scott. 1967. Concentrations of Cr, Ag, Mo, Ni, Co, and Mn in suspended material in streams. Environ. Sci. Technol. 1: 940.

U.S. Department of Health, Education, and Welfare. 1962. Public Health Service drinking water standards. HEW Publ. 956. U.S. Dep. Health, Education, and Welfare, Washington, D.C.

U.S. E.P.A. Undated. Comparison of NTAC, NAS, and proposed EPA numerical criteria for water quality. U.S. Environ. Prot. Agency, Washington, D.C.

U.S. E.P.A. 1976. National interim primary drinking water regulations. EPA-570/9-76-003. U.S. Environ. Prot. Agency, Off. of Water Supply.

Valente, P., and J.L. Axelrod. 1978. Acute leukopenia associated with silver sulfadiazine terapy. Jour. Trauma 18: 146.

Van Campen, D.R. 1966. Effects of zinc, cadmium, silver and mercury on the absorption and distribution of copper-64 in rats. Jour. Nutr. 88: 125.

Vanselow, A.P. 1966. Chapter 26. Silver. In: H.D. Chapman, ed. Diagnostic criteria for plants and soils. Univ. Calif., Div. Agric. Sci., Riverside, Calif. p. 405.

Van Vleet, J.R. 1976. Induction of lesions of selenium-vitamin E deficiency in pigs fed silver. Am. Jour. Vet. Res. 37: 1415.

Van Vleet, J.R. 1977. Protection by various nutritional supplements against lesions of selenium-vitamin E deficiency induced in ducklings fed tellurium or silver. Am. Jour. Vet. Res. 38: 1393.

Vinogradov, A.P. 1953. The elementary chemical composition of marine organisms. Sears Foundation for Marine Research, Yale Univ., New Haven, Conn.

Von Rosen, G. 1954. Breaking of chromosomes by the action of elements of the periodical system and by some other principles. Hereditas 40: 258.

Van Rosen, G. 1957. Mutations induced by the action of metal ions in Pisum. Hereditas 43: 644.

Wagner, P.A., et al. 1975. Alleviation of silver toxicity by selenite in the rat in relation to tissue glutathione peroxidase. Proc. Soc. Exp. Biol. Med. 148: 1106.

Wahlberg, J.E. 1965. Percutaneous toxicity of metal compounds. A comparative investigation in guinea pigs. Arch. Environ. Health 11: 201.

Wall, F.E. 1957. Chapter 21. Bleaches, hair colorings, and dye removers. In: E. Sagarin, ed. Cosmetics: science and technology. Interscience Publishers, Inc., New York, N.Y. p. 479.

Wall, F.E. 1972. Chapter 23. Bleaches, hair colorings, and dye removers. In: M.S. Balsam, E. Sagarin, S.D. Gershon, S.J. Strianse, and M.M. Rieger, eds. Cosmetics: science and technology, 2nd ed., Vol. 2. Wiley-Interscience, a Div. of John Wiley and Sons, Inc., New York, N.Y. p. 279.

Warburton, J.A. 1969. Trace silver detection in precipitation by atomic absorption spectrophotometry. Jour. Appl. Meteorol. 8: 464; Chem. Abstr. 1969. 71: 523.

Ward, N.I., et al. 1977. Silver in soils, stream sediments, waters and vegetation near a silver mine and treatment plant at Maratoto, New Zealand. Environ. Pollut. 13: 269.

Weissman, R.V. 1975. Caution and restraint (letter). Jour. Am. Dent. Assoc. 91: 736.

West, H.D., and H. Goldie. 1956. Topical localization in mouse of radioactive silver oxide $(Ag^{111})_2O$ introduced by various routes. Proc. Soc. Exp. Biol. Med. 92: 116.

West, H.D., et al. 1950. In vivo localization of radioactive silver at predetermined sites in tissue. Am. Jour. Roentgenol. Radium Ther. 64: 831.

Whanger, P.D., et al. 1976a. Effects of selenium, cadmium, mercury, tellurium, arsenic, silver and cobalt on white muscle disease in lambs and effect of dietary forms of arsenic on its accumulation in tissues. Nutr. Rep. Int. 14: 63.

Whanger, P.D. 1976b. Selenium versus metal toxicity in mammals. In: Proc Symp. on Selenium-Tellurium in the Environ., Univ. Notre Dame, May 11-13, 1976. Industrial Health Foundation, Inc., Pittsburg, Penn. p. 234.

Winell, M. 1975. An international comparison of hygienic standards for chemicals in the work environment. Ambio 4: 34.

Wood, M. 1965. Silver nitrate and burns--caution!!! Ariz. Med. 22: 817.

Wyckoff, R.C., and F.R. Hunter. 1956. A spectrographic analysis of human blood. Arch. Biochem. 63: 454.

Wysor, M. 1975a. Antimalarials: screening of (orally administered) silver sulfonamides against _Plasmodium berghei_. Chemotherapy 21: 284.

Wysor, M.S. 1975b. Orally administered silver sulfadiazine--chemotherapy and toxicology in CF-1 mice--_Plasmodium berghei_ (malaria) and _Pseudomonas aeruginosa_. Chemotherapy 21: 302.

Wysor, M.S. 1977. Administration of silver sulfadiazine and radioactive derivatives thereof. U.S. Pat. 4,020,150. April 26, 1977.

Yoshikawa, H. 1970. Preventive effect of pretreatment with low dose of metals on the acute toxicity of metals in mice. Ind. Health 8: 184.

Zapadnyuk, V.I., et al. 1973. O biologicheskoi roli medi i serebra i vliyanii ikh na passivno-oboronitel'nuyu reaktsiyu belykh krys (Biological role of copper and silver and their effect on the passive defense reactions of white rats). Vodopodgot. Ochistka Prom. Stokov. 10: 91.

Zech, P., et al. 1973. Syndrome nephrotique avec depot d'argent dans les membranes basales glomerulaires au cours d'une argyrie (Nephrotic syndrome with silver deposits in the glomerular basement membranes during argyria). Nouv. Presse. Med. 2: 161.